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THE SOCIAL INCIDENCE OF RHEUMATIC HEART DISEASE.

A STATISTICAL STUDY IN YALE UNIVERSITY STUDENTS.

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IT has been tacitly accepted by many that rheumatic fever is a disease which finds its highest incidence among individuals living under poor hygienic conditions, and that these poor living conditions are generally an expression of limited economic means. Unfortunately, few statistical data exist in the United States on which to base this contention, although it would seem to be a point of considerable import. From England we have Miller's[1] statement that: "Although technically the rheumatic infection may not be a 'poverty disease' in that its frequency does not seem to follow absolutely the variations in degree of poverty, yet nothing is more certain than that it is a disease of the poorer classes." Glover[2] also believes that: "No disease has a clearer cut 'social incidence' than acute rheumatism, which falls perhaps thirty times as frequently upon the poorer children of the industrial town, as upon the children of the well-to-do." Statistics[3] to bear out the contention that rheumatic fever is a disease seen with great frequency

in hospital wards, as opposed to private pavilions and consulting practice, show that among 1000 children from the Outpatient Department of King's College Hospital, London, the incidence of those who showed evidence of acute rheumatism was 13.1 per cent, whereas among 700 children from private practice the incidence was only 0.7 per cent. Other British observations on the subject include those of Hutchison,[4] who comments on the differences between the incidence of rheumatic fever in private practice and in hospital wards; of Coombs,[5] that it is quite certainly a rare disease among the well-to-do; and of Campbell and Warner,[6] who have the impression that the poorest are most commonly affected. The last statement, however, is qualified by some observers, reflecting Miller's views already quoted, that the disease tends to be more frequent among children of the decent poor, than among the squalid.[7]

Evidence which also bears on the factor of poverty is the oft-mentioned observation that, in certain boarding or public schools of England, such as Eton College and Beaumont College, attended by sons of the well-to-do, the incidence of rheumatic fever is very low in the school populations, in spite of the fact that the schools are situated in districts in which the disease is prevalent.

From other countries the importance of poverty and all its attendant conditions as a predisposing factor in rheumatic fever has not been emphasized with so much vigor. However, Nobel,[8] in Germany, believes that rheumatism is a disease of the poor. In the United States Faulkner and White[9] obtained data from colleges and private preparatory schools and concluded that rheumatic infections and rheumatic heart disease were less common among this comparatively well-to-do group. Swift[10] states that: "apparently, poverty, malnutrition, and unhygienic surroundings furnish the most favorable human soil for the development of this infection. Many cases are seen, however, among well-to-do members of society."

In the face of these statements, backed by more than suggestive evidence, it would seem important to go further into an analysis of the situation in this country. Does poverty really predispose to rheumatic fever, and, if so, to what extent? The answer is important because such facts concern an evaluation of environmental influences which predispose to this obscure disease, and knowledge of them may be of some value in the field of prevention. For their determination we would like to know the incidence of rheumatic fever among different strata of society in various widely scattered communities. At the moment, however, such data are not available, for, on the one hand, the stratification of a given American population according to different social and economic standards is not as clearly defined as in England; on the other hand, the incidence of rheumatic fever, or the mortality rates justly attributed to this disease, are practically unknown quantities in

this country. To our knowledge, it is a reportable disease only in a few countries or communities, and unfortunately rheumatic lesions are not accurately reflected in mortality statistics.

Perhaps the nearest practical approach which at present can be made to an estimation of the incidence of this disease is the determination of the incidence of rheumatic cardiac lesions in a given population. We recognize fully that the incidence of rheumatic fever and that of rheumatic heart disease may be two quite different things and that the rate of development of the cardiac manifestations of rheumatic fever may be an indication of the type of therapy to which rheumatic patients are subjected, rather than an expression of the actual incidence of rheumatic fever. However, even if it were possible to obtain data on the incidence of *rheumatic fever* in a few selected groups of individuals we would not have any general figures with which to compare them, whereas rough statistics on the incidence of *heart disease* in various populations do exist.

With this thought in mind we have recently reviewed the incidence of rheumatic heart disease in a group of Yale University undergraduate students, as the first of a series of studies which we hope to make on the incidence of rheumatic heart disease in differently selected populations. With the University population we are dealing with a selected group of young male adults, most of whom come from the northeastern part of the United States, and among whom there is a high percentage from so-called upper economic strata. It is our immediate purpose to compare the incidence of rheumatic heart disease in this group with other groups, selected from the literature, and also to analyze roughly the distribution of rheumatic cardiac disease according to the economic status of the men within the group itself. In other words, the questions to be answered from these data are: (*a*) Is rheumatic heart disease as common among our group of University students as it is supposed to be among individuals of similar age from other walks of life; (*b*) is there a higher incidence of rheumatic heart disease among students representing poorer families than among those representing families which are better-to-do? The choice of the student group as a favorable population in which to pursue such a study lies mainly in the fact that it contains a fair number of representatives of well-to-do families, a feature not present in groups of industrial employees, recruits, etc., which have been subjected to similar incidence studies. Whatever results are obtained from such a well-to-do group should, however, be eventually evaluated by comparison with incidence figures drawn from the poorer sections of city and rural districts.

Methods. *Selection of Cases.* To obtain our data, the medical histories of 7914 undergraduate students and 4455 male graduate students were reviewed. The records examined, which are compiled

and kept by the Yale University Department of Health, covered all undergraduates enrolled in the classes of 1920 to 1930, inclusive, and all male graduate and professional school students matriculating at the University during the period from 1920 to 1930, who had undergone physical examinations conducted by the University Department of Health during their period of matriculation. Each undergraduate student's record includes from one to four complete, annual, physical examinations, together with form letters from the parents and a completed form by the student, briefly describing the past medical history. In a high percentage of the group are also included records of illness contracted during their period of matriculation.

The number of complete physical examinations per man varied somewhat during this period. Members of the undergraduate classes of 1920 and 1922, inclusive, underwent a single physical examination; those of the classes of 1923 and 1924 underwent two examinations, at the beginning and end of their course, respectively; those of the classes of 1925 to 1930, inclusive, underwent four examinations, one during each of the years in which the individual was enrolled as an undergraduate. It is evident, therefore, that a progressive increase in the thoroughness in which the physical data were obtained exists.

The histories of the entire group were first gone over by an experienced clerk,* and from them all those were selected in which were recorded cardiac lesions, or abnormalities of cardiac function of any kind, exclusive of so-called functional cardiac murmurs. The selected cardiac records were then gone over by one of us, and from them were chosen those cases which could be logically interpreted as examples of rheumatic heart disease. The diagnosis of rheumatic heart disease had not been made in many instances by the examining physician; such terms as mitral regurgitation, chronic endocarditis, etc., were employed instead, but in a surprising number of what might have been questionable cases the student gave a history of rheumatic fever. Clinical judgment was required in order to arrive at a decision in a fair number of cases. In these the following criteria were employed: All cases of mitral stenosis were accepted as examples of rheumatic heart disease, all cases of endocarditis, and of mitral and aortic insufficiency, in which the student gave a history of either rheumatic fever or heart trouble following scarlet fever were also accepted. The remaining number of questionable cases turned out to be relatively small, for in most instances the examining physicians had made every effort to determine whether or not suggestive signs were actual manifestations of organic heart disease, and in nearly all such instances the student had been examined by a heart specialist.

* We are particularly indebted to Miss Mildred A. Mahoney for her assistance to us in this aspect of the work.

Control Disease Groups. It is difficult to find a common clinical condition which is truly comparable to inactive rheumatic heart disease, that is, a common disease which is generally contracted during childhood and in which evidence of old (or active) lesions can be detected on physical examination during young, adult life. Although neither of the two control conditions which we finally selected proved truly satisfactory, they seemed to be the best at our disposal—they included: (1) Clinical tuberculosis, and (2) allergic diseases, such as bronchial asthma and hay fever. In the first, *i. e.*, clinical tuberculosis, we recognize that straitened economic circumstances may play a heavy predisposing rôle which can be reflected in incidence statistics; in the second, *i. e.*, allergic diseases, it has been maintained that the reverse is true, namely, that these conditions find a higher incidence among better-to-do members of society.* The criteria on which these control cases were selected from the group of 7914 undergraduate students were as follows: (1) Tuberculosis. This included students who developed clinical tuberculosis during their college course and those who showed evidence of old tuberculosis detectable by physical examination, or who gave an unequivocal history of having had clinical tuberculosis and having been under treatment. In all of the latter instances, letters from physicians or sanatoria referring to the patient's condition accompanied the student's history. (2) Allergic conditions. This included students who showed active manifestations of these conditions during their college course, and those who gave a history of severe, or moderately severe, asthma or hay fever within 5 years prior to their admission to the University.

Method of Evaluating Financial Status. Three methods of approach were chosen to determine the financial status of the families from which students with rheumatic heart disease or the control diseases came:

(*a*) The character of the preparatory schools which they had attended. These were arbitrarily divided into four groups: (1) Boarding schools—Grade I, more expensive; (2) boarding schools—Grade II— less expensive; (3) private day schools; (4) high schools.

(*b*) Whether or not the student had been self-supporting during his period of matriculation, *i. e.*, had applied to the University Bureau of Appointments during his college course.

(*c*) Whether or not he had held a scholarship in order to defray tuition expenses.

As about 90 per cent of first attacks of rheumatic fever seem to

* This point does not seem to have been emphasized in many of the recent works which we have consulted on asthma and hay fever and, in fact, is denied in one of them;[11] but the statement, that bronchial asthma and hay fever is an affection which belongs peculiarly to the upper ranks of society, may be found in many of the older textbook articles, such as those in Allbutt's System of Medicine, 1898; Nothnagle's Encyclopedia of Practical Medicine, American edition, 1902; and Osler's Modern Medicine, 1907.

occur before the age of 15 years,[12,13] we were more interested in ascertaining the financial status of the student's family during his childhood than the financial status of the student himself while a matriculant. In this respect method (*a*), *i. e.*, the preparatory school grading, may be a little more adequate than methods (*b*) and (*c*). In criticism of all three methods it must be said that they have obvious limitations. The figures obtained can only be judged insofar as they can be compared with similar figures obtained from the total contemporary University population, and, if these methods are at all adequate, the control diseases should give significant, predictable deviations from the mean.

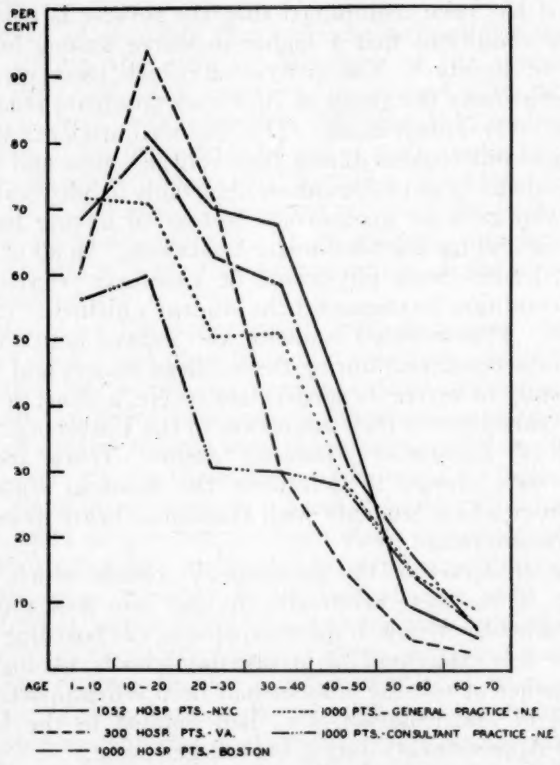

FIG. 1.—The percentile age distribution of rheumatic heart cases in five groups of cardiac patients.

The Incidence of Rheumatic Heart Disease Among Young Male Adults in the United States. There are few observations recording the incidence of rheumatic heart disease in various American populations with which our results can be compared and, so far as we can find, there are none which actually record direct observations on the actual incidence of rheumatic heart disease among large groups of young male adults. One may arrive, however, at an

indirect estimation from statistics based on the incidence of cardiac disease of all types. Roughly it has been accepted that the total incidence of heart disease *of all types* among public school children in eastern North American cities lies somewhere between 6 and 20 per 1000; among young North American adults, *i. e.*, under 30 years, between 15 and 34 per 1000.* These various estimates are dependent upon the manner in which a given population has been selected—its age distribution, its geographic location and the diagnostic criteria employed in determining what constitutes cardiac disease. Unfortunately we cannot accurately evaluate these variants unless they are all specified in each report, which does not happen to be the case. Space does not permit a discussion of the relative importance which each may play, but one of us has assembled data in another publication which deals with this aspect of the problem, to which the reader may be referred.[15] There is, however, one variant, namely, age, which lends itself to analysis more readily than some of the other variants, and which is furthermore an expression of the different etiologic types of heart disease within the group. For instance, we may be sure that in the northeastern part of the United States most cardiac disease which occurs in individuals under 25 years is due to rheumatic fever, if we draw upon the figures of Wyckoff and Lingg,[16] Wood, Jones and Kimbrough,[17] and White and Jones,[18] whose observations in various selected cardiac populations have been charted in Fig. 1. There are wide differences in some of the determinations listed here, but, by and large, all tend to emphasize the importance of rheumatic fever as a cause of heart disease in the first three decades of life.

TABLE 1.—ESTIMATED INCIDENCE OF RHEUMATIC HEART DISEASE AMONG GROUPS OF YOUNG ADULTS.

Character of population.		Size of population.	Age.	Observed incidence of heart disease per 1000.	Estimated per cent of total heart disease which is rheumatic.	Estimated incidence rheumatic heart disease per 1000.
Troops . .	United States Draft, 1918[19]	2,510,751	21 to 30	26.26	60	15.7
	North—White	10,005	21 to 30	34.15	60	20.4
	South—White	10,571	21 to 30	24.60	60	14.7
	South—Negro	5,239	21 to 30	29.07	60	17.8
	East	7,934	21 to 30	35.56	60	21.3
Insurance .	Metropolitan Life Insurance Company 1921[20]	861	Under 25	17.00	65	11.0
Industry (male)	Garment workers[21]	2,107	80% below 40	23.00	56	12.8
	Working boys (N. Y. C.) 1930[22]	2,691	14 to 17	16.00	77	12.3
Students .	Harvard University 1915[23]	662	18	19.4†	72+	13.9+

* Cohn has assembled various incidence figures for heart disease in his excellent review of Heart Disease from the Point of View of the Public Health.[14] Most of our general incidence data have been derived from his paper, supplemented by additional data which one of us has assembled elsewhere.[15]

† Valvular disease of the heart.

Included in Fig. 1 is a series of 300 patients from Virginia, in which, although the total incidence of rheumatic heart disease in this group is lower, the age curve conforms to that found in the North.

Armed with these facts we may then approach statistics on the incidence of cardiac disease in large groups comparable as to age and sex with those of our University students. These appear in Table 1. Here are recorded the observed incidence of heart disease in various populations, together with estimates of the expected percentages (taken from data in Fig. 1) of *rheumatic heart disease* in the different age groups. We assume as a conservative estimate that, of the heart disease occurring between the ages of 15 and 20 years, at least 75 per cent is due to rheumatic fever; between the ages of 20 and 25 years, 65 per cent; between the ages of 25 and 30 years, 55 per cent. Such estimates give us incidence figures for rheumatic heart disease in the populations listed in Table 1 (roughly representing the age group of 14 to 30 years). They prove to be between 11 and 21.3 per 1000. The lowest figure is recorded among individuals applying for insurance, and the highest among men from the eastern part of the United States who were examined by the Draft Boards. On this basis as a conservative average for the incidence of rheumatic heart disease among young adult men between the ages of 18 and 25 years, who represent the general population of the northeastern part of the United States, one might take the figure of 15 per 1000, and it is with this figure that our subsequent studies in the University group will be compared.

Results. *Age Distribution of the Student Population of Yale University.* In Fig. 2 is shown the age distribution of undergraduate and graduate students attending Yale University during the years of 1920 to 1930. The graphs record the age on entering the University. One may assume that the average leaving age is approximately 3½ years higher for undergraduates and 3 years for the graduate and professional school students. In the first group, therefore, we are dealing with a population in which most of the students fall between the ages of 17 and 24 years; in the second, between the ages of 19 and 30 years.

Incidence of Rheumatic Heart Disease Among Yale University Students. The observed incidence of rheumatic heart disease, which we obtained by methods outlined above, proved to be 8.2 per 1000 for the undergraduate group and 11.4 per 1000 for the graduate group. (See Table 2.) Both of these figures lie below that which we have assumed to be the average rate for the general population in the northeastern part of the United States, namely, 15 per 1000. The explanation of the higher incidence between the undergraduate and graduate group is not clear. Obviously the latter are older, as shown in Fig. 2, but there are also certain differ-

ences in the general make-up of the two groups. One of these differences is perhaps best expressed by a fact, which will be enlarged upon later, that among the undergraduate students approximately 75 per cent have entered college from private schools as opposed to high schools; whereas, among the graduate and professional students we find that almost 60 per cent of them had entered college from high schools. It is also pertinent to consider this observed higher incidence of rheumatic heart disease in graduate students in the light of similar experiences with tuberculosis, for it is our belief that, in spite of expected differences attributable to age, clinical tuberculosis also finds a much higher incidence

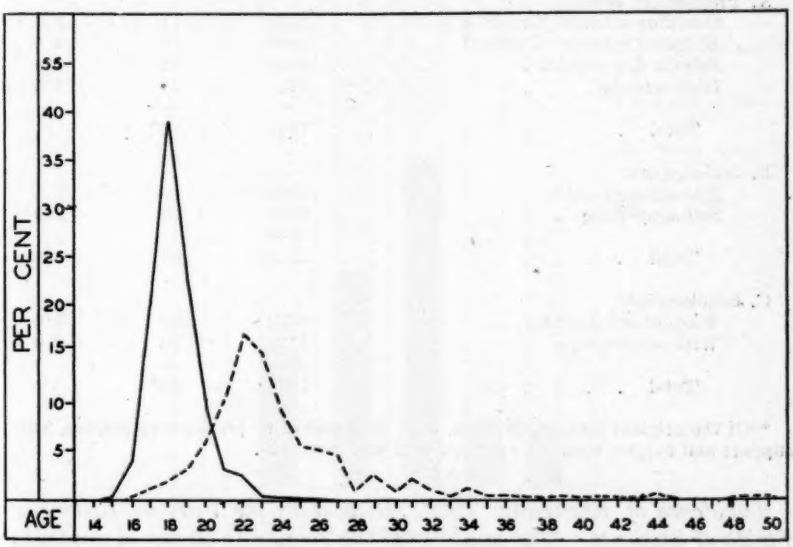

FIG. 2.—The age distribution of Yale University students. The broken line represents the entering age of graduate students; the solid line, of undergraduates.

among the graduate students of Yale University than among the undergraduates.* In the present study of our control groups, for instance, which has been based on criteria mentioned above, the case rate of tuberculosis among graduate students was more than double that for the undergraduates.

From figures in Table 1 it will be seen that in 1915 the incidence of valvular disease of the heart among 695 Harvard freshmen was found by Lee[23] to be 19.4 per 1000, a figure which is far higher than that found among our undergraduate or graduate students. Whether there are certain inherent differences in the two University

* Recent observations by Dr. E. L. Opie and his associates also point to a considerably higher incidence of tuberculosis among medical students than among college students.[24]

populations or not, we are not prepared to say, any more than we are prepared to claim leadership on the basis of these figures in a health contest between these two institutions in which rivalries of other types have been tested before.

TABLE 2.—RHEUMATIC HEART DISEASE INCIDENCE IN STUDENT POPULATION.

Character of student population.	No. in group.	No. of cases rheumatic heart disease.	Rate per 1000.
Undergraduates—Classes 1920 to 1930	7914	65	8.2
Graduate students, 1920 to 1930	4455	51	11.4
Undergraduates classified according to:			
A. Preparatory schools:			
Boarding schools—Grade I	1878	11	5.8
Boarding schools—Grade II	1996	11	5.5
Private day schools	1809	12	6.6
High schools	2231	28	12.5
Total	7914	62*	
B. Self-support:			
Nonself-supporting	4995	37	7.4
Self-supporting	2919	26	8.9
Total	7914	63*	
C. Scholarships:			
Without scholarships	6791	53	7.8
With scholarships	1123	10	8.9
Total	7914	63*	

* Of the original total of 65 cases, data with regard to preparatory schools, self-support and tuition were not available in 2 or 3 instances.

Incidence of Rheumatic Heart Disease in the Various Economic Strata of Students.—The analysis of the economic status of students has been confined to the undergraduate group alone.

(*a*) *Preparatory Schools.* Our first attempt to grade the economic status of the families of students with rheumatic heart disease has been based on the character of the schools at which individual boys had prepared for college. As already stated, this is not an accurate index of affluence or penury, for many sons of rich manufacturers attend high schools, and many sons of poor college professors attend boarding schools in which the tuition fees are quite out of keeping with the professor's salary. Furthermore, an element of selection may enter the problem as boys with rheumatic heart disease may not be sent away to boarding school, or, for that matter, to college with the same frequency as their healthier fellows. Nevertheless, these attempts to grade the families on the preparatory school basis seem to be significant, if only from the fact that in the case of our control diseases, *i. e.*, tuberculosis, bronchial asthma and hay fever, in one of which the effect of economic status has been

particularly recognized, the results fall out as one might have predicted.

Our preparatory school findings appear in diagrammatic form in Fig. 3. Here the average distribution of the type of schools which had been attended by undergraduate students of the classes 1920 to 1930 is shown in the first left-hand column. It will be seen that only 26 per cent of the 7914 men in this group had entered college directly from high schools, while almost 50 per cent had entered from boarding schools. Of the small group of students with rheumatic heart disease, shown in the next column, 45 per cent

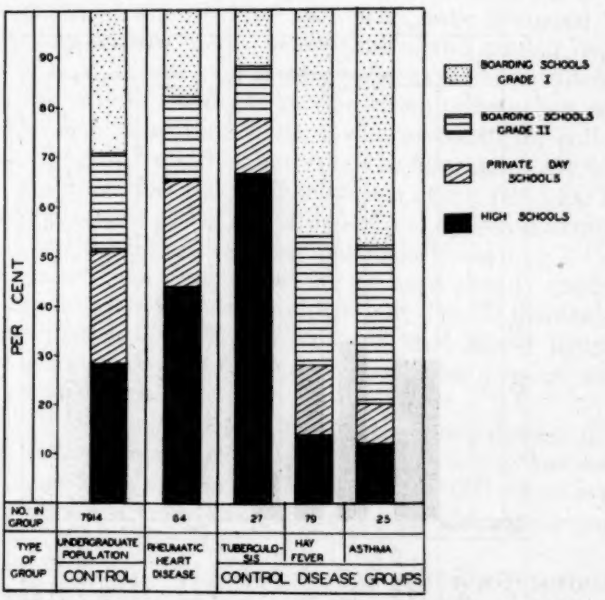

FIG. 3.—The relative percentages of preparatory schools represented by undergraduates of the Classes of 1920 to 1930, as compared with similar percentages from a group of students with rheumatic heart disease, and other control disease groups.

had come from high schools, and of the students with tuberculosis, 65 per cent had come from high schools. In sharp contrast stands the group of men with allergic diseases in which only 12 per cent had come from high schools. This last finding would seem to bear out the contentions which appear in older textbook articles on bronchial asthma and hay fever, to which we have already referred. We recognize, of course, that our method of approach in these latter conditions may not give us a true indication of actual incidence, but rather the incidence of cases of bronchial asthma and hay fever concerning which either a physician was consulted, or the patient was sufficiently aware of his symptoms to list them in his past

medical history. The same may be said, of course, of our tuberculosis controls.

If our results are expressed in a different manner, as shown in Table 2, we find that the incidence of rheumatic heart disease in boys who had attended expensive boarding schools is only 5.8 per 1000, in contrast to 12.5 per 1000 among boys from high schools.

(*b*) *and* (*c*). *Self-supporting and Scholarship Students versus Students Who Are Non-self-supporting and Without Scholarships.* In Fig. 4 are shown the relative percentages of men in the total undergraduate population who were wholly or partially contributing to their own support, and also those who held scholarships to

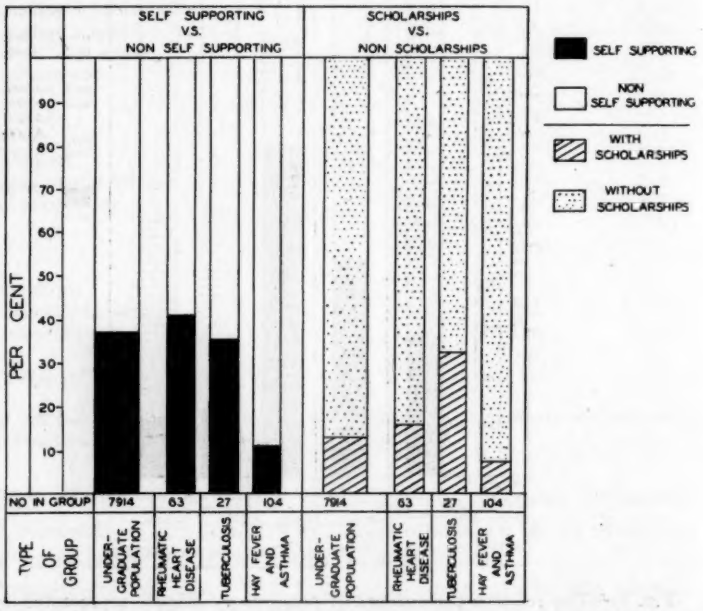

FIG. 4.—The relative percentages of self-supporting students, and students with scholarships in the undergraduate classes of 1920 to 1930, as compared with students with rheumatic heart disease, and other control disease groups.

defray tuition expenses, as compared with these conditions in students with rheumatic heart disease and the other control disease groups. Here again these two methods of evaluating the economic status of students have obvious limitations. In particular, one might well say that the holding of a scholarship is supposedly first and foremost an attribute of mental ability rather than that of limited means. Nevertheless, the control diseases fall out more or less according to the expected ratio, although the demonstration is by no means so marked as in the grading on the basis of preparatory schools. In the case of the rheumatic group it will be seen in both instances, that, if these criteria are a measure of financial

status, the student with rheumatic heart disease is a shade poorer than the average student, but it is questionable whether such minor differences are of any significance. These same data expressed in a different manner also appear in Table 2.

Discussion. By and large, one may conclude from a study of this type that there is some evidence to support the fact that the incidence of rheumatic heart disease is lower among well-to-do individuals than it is among the rank and file, but this feature has proved to be a more difficult thing to prove by the present methods employed than we had anticipated. Within the limitations of our methods one can at least say that the incidence of rheumatic heart disease in a group of almost 4000 men who have prepared for college at boarding schools is well below that of the general population; in fact, it is almost one-third of the expected incidence. Furthermore, the rate or incidence in this group is less than one-half that of the rate in a group of men who prepared for college at high schools. Apart from this, however, the figures are not very significant. It is true that the total incidence of 8.2 per 1000 for the whole undergraduate group is well below the expected average of 15 per 1000, but the difference is not particularly striking. Certainly the statement from England, which we have already quoted, that there is no disease which has a clearer cut "social incidence" than acute rheumatism, is not strikingly reflected in our figures, but we do not as yet have data from poverty-stricken districts with which we may test this thesis.

Conclusions. 1. The incidence of rheumatic heart disease in a group of 7914 undergraduate students of Yale University has been found to be 8.2 per 1000, as compared with 15 per 1000 which is an average figure obtained from statistics of comparable age groups of individuals in other walks of life.

2. Among the men in this group who had attended expensive boarding schools the incidence was only 5.8 per 1000 as compared with 12.5 per 1000 among those from high schools.

3. The contention that rheumatic fever is a disease which finds a lower incidence among people of ample means finds support in these observations.

4. According to the methods employed the factor of poverty does not, however, seem to be as important a predisposing rôle in determining the incidence of rheumatic heart disease as it does in clinical tuberculosis.

BIBLIOGRAPHY.

1. Miller, R.: Report on the Environmental and Other Predisposing Causes of Rheumatic Infection, Suppl., Brit. Med. J., July 3, 1926.

2. Glover, J. A.: Milroy Lectures on the Incidence of Rheumatic Diseases: I. Incidence of Acute Rheumatism, Lancet, 1930, **1**, 499.

3. Child Life Investigations: Social Conditions and Acute Rheumatism, Special Report Series of the Medical Research Council, No. 114, London, His Majesty's Stationery Office, 1927.

4. Hutchison, R.: The Value of Pulse Charts in Acute Carditis in Childhood, Lancet, 1922, **1**, 1086.

5. Coombs, C. F.: Rheumatic Infection of Childhood, Lancet, 1927, **1**, 579, 634.
6. Campbell, M., and Warner, E. C.: A Study of Rheumatic Disease in Children, Lancet, 1930, **1**, 61.
7. Thomson, A. P.: Discussion on Rheumatic Infection in Childhood, Brit. Med. J., 1925, **2**, 794.
8. Nobel, E.: Statistik und Prophylaxe der Klappenfehler, Wien. klin. Wchnschr., 1928, **41**, 125.
9. Faulkner, J. M., and White, P. D.: The Incidence of Rheumatic Fever, Chorea and Rheumatic Heart Disease With Especial Reference to Its Occurrence in Families, J. Am. Med. Assn., 1924, **83**, 425.
10. Swift, H. F.: Rheumatic Fever, Cecil's Textbook of Medicine, Philadelphia, W. B. Saunders Company, 1927.
11. Coca, A. F., Walzer, M., and Thommen, A. A.: Asthma and Hay Fever in Theory and Practice, Springfield, Ill., Charles C Thomas, 1931, p. 178.
12. Wilson, M. G., Lingg, C., and Croxford, G.: Statistical Studies Bearing on Problems in the Classification of Heart Disease: III. Heart Disease in Children, Am. Heart J., 1928–1929, **4**, 164.
13. Paul, J. R.: Age Susceptibility to Familial Infection in Rheumatic Fever, J. Clin. Invest., 1931, **10**, 53.
14. Cohn, A. E.: Heart Disease From the Point of View of the Public Health, Am. Heart J., 1927, **2**, 275, 386.
15. Paul, J. R.: The Epidemiology of Rheumatic Fever: A Preliminary Report With Special Reference to Environmental Factors in Rheumatic Heart Disease and Recommendations for Future Investigations, New York, Metropolitan Life Insurance Company Press, 1930.
16. Wyckoff, J., and Lingg, C.: Statistical Studies Bearing on Problems in the Classification of Heart Disease: II. Etiology of Heart Disease, Am. Heart J., 1926, **1**, 446.
17. Wood, J. E., Jones, T. D., and Kimbrough, R. D.: The Etiology of Heart Disease, Am. J. Med. Sci., 1926, **172**, 185.
18. White, P. D., and Jones, T. D.: Heart Disease and Disorders in New England, Am. Heart J., 1928, **3**, 302.
19. Love, A. G., and Davenport, C. B.: Defects Found in Drafted Men, Washington, D. C., Government Printing Office, 1920.
20. Dublin, L. I., Fisk, E. L., and Kopf, E. W.: Physical Defects as Revealed by Periodic Health Examinations, Am. J. Med. Sci., 1925, **170**, 576.
21. Schereschewsky, J. W., and Tuck, D. H.: Studies in Vocational Diseases: I. The Health of Garment Workers, Public Health Bull., No. 71, Washington, D. C., 1915.
22. Metropolitan Life Insurance Company, Statistical Bull., 1930, **11**, No. 2.
23. Lee, R. I.: Preventable Heart Disease, Boston Med. and Surg. J., 1915, **173**, 157.
24. Hetherington, H. W., McPhedran, F. M., Landis, H. R. M., and Opie, E. L.: Tuberculosis in Medical Students, Trans. Assn. Am. Phys., 1931, **46**, 237.

THE IMMEDIATE CAUSES OF DEATH IN CANCER.

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But little information exists as to the actual immediate causes of death in cases of cancer. This is largely because in mortality statistics cancer appears alone as the cause of death in cases of that disease. In the course of a study of the cases of cancer which

came to autopsy in the laboratories of the New England Deaconess Hospital, the Collis P. Huntington Memorial Hospital, the House of the Good Samaritan and the Pondville State Hospital, the immediate cause of death in each case was determined as accurately as possible from a study of both the clinical record and the postmortem protocol of the patient.

In the present paper the findings in 500 cases of carcinoma are presented. These cases were selected at random, but sarcoma, lymphoblastoma, leukemia, etc., have been excluded. There are practically no cases of cancer in children included.

By the use of material from four hospitals the variation in picture due to the tendency of certain hospitals to have more of given types of cases than others has been largely compensated for. Moreover, among these hospitals there are not only beds for early or "active" cases of cancer but for terminal-care cases as well, so that the proportion of deaths due to accidents of treatment is not as large as it appears to be in statistics from a general hospital. A certain number of deaths of this latter type is inevitable in view of the very extensive condition of the disease in many cases at the time they present themselves for treatment.

The distribution of cases in this study is compared in Table 1 with that in the Massachusetts mortality statistics for 1930. It will be noted that the number of cases primary in the buccal cavity, skin, female genitalia and breast are definitely higher in the study group, and cancer primary in the stomach and liver and unspecified organs much lower. This distribution is to be expected, as the groups of stomach and liver and of unspecified organs are naturally abnormally large in mortality returns based largely on clinical observations. This discrepancy is particularly noted in the group of cancers of the stomach and liver, which comprises over one-fourth of the general group and only one-ninth of the study group.

TABLE 1.—DISTRIBUTION OF FATAL CASES OF CANCER BY PRIMARY SITE.

	Total cases.	Buccal cavity, per cent.	Stomach and liver, per cent.	Peritoneum, intestine and rectum, per cent.	Female genitals, per cent.	Breast, per cent.	Skin, per cent.	Other or unspecified organs, per cent.
Mass. statistics, 1930	5813	3.2	28.4	19.2	13.4	11.1	1.6	23.2
Study group	500	11.0	11.0	18.0	20.0	17.4	4.6	18.0

Cancer of the buccal cavity and of the skin is somewhat heavily weighted in the study group, because of the numbers of these cases treated in the outpatient department of the Huntington Hospital, some of which fail to respond to treatment and are later admitted to the house.

The distribution of cases in the study series is not too far at

variance with that given for the population of Massachusetts and apparently represents a fair sample of the fatal cases of cancer.

The most commonly occurring of the various causes of death is cachexia. This term was utilized only in those instances where the clinical course of the disease was characterized by progressive wasting and weakness, accompanied by increasing anemia. Cachexia has not been considered the immediate cause of death if any lesion sufficient in itself to be fatal has been discovered. It may, therefore, be regarded as considerably more frequent than is recorded here. It is striking that in almost all instances of death due to cachexia, of which there were 114 in the present series (more than 22 per cent), there had been considerable necrosis of the tumor tissue, due either to ulceration and secondary infection or to interference with the blood supply of the tumor.

In a number of cases where death was due to definite anatomic causes cachexia was present to a greater or less degree, but in most of these the cachexia could be definitely established as secondary to sepsis, hemorrhage or other lesion which was considered as the immediate cause of death.

Startling to the novice is the large number of fatal cancer cases in which excellent nutrition and not infrequently obesity are maintained to the end.

In carcinoma of the breast and carcinoma of the stomach one finds the largest proportion of deaths from cachexia (33.3 and 45.2 per cent, respectively), and in carcinoma of the bladder the least (4.3 per cent). (Table 2.) When the cases of cachexia are studied in relation to organs involved (Table 3) the rectum-colon group becomes even more important than the stomach. The carcinomas of the breast, as may be seen from Table 3, caused over one-fourth of all the deaths from cachexia. The next most frequent lesions were carcinoma of the rectum and colon with 17.5 per cent, and of the stomach with 16.7 per cent. The bladder and the prostate each were the primary sites in less than 1 per cent of the cases dying from cachexia.

The relatively high incidence of pneumonia (14 per cent), particularly bronchopneumonia, would be expected in a group such as this where the age level is relatively high and resistance to infection is naturally considerably lowered. Bronchopneumonia is much more common than lobar. There were 64 cases of bronchopneumonia and only 6 cases of lobar pneumonia. These cases of lobar pneumonia may be regarded as intercurrent infections, having very little immediate relation to the underlying disease process. With their almost inevitable interference with the respiratory passages and the excellent opportunity for inhalation and aspiration of foreign material, the carcinomas of the lip and pharynx provided 24.3 per cent of the cases of pneumonia. Moreover, in this same group of cases pneumonia is by far the most common single cause of death, amounting to 36.2 per cent. (Table 2.)

TABLE 2.—THE FREQUENCY OF COMMON CAUSES OF DEATH IN CARCINOMA OF SPECIFIED ORGANS.

	Total number.	Cachexia.		Pneumonia.		Renal insufficiency.		Peritonitis.		Pulmonary insufficiency.		Embolus (pulmonary).		Other causes.	
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Bladder	23	1	4.4	2	8.7	17	73.9	1	4.4	—	—	1	4.4	1	4.4
Breast	87	29	33.3	10	11.5	2	2.3	3	3.5	19	21.8	3	3.5	21	24.1
Cervix uteri	64	10	15.6	6	9.4	27	42.2	9	14.1	1	1.6	3	4.7	8	12.5
Colon and rectum	90	20	22.2	13	14.4	1	1.1	21	23.3	—	—	5	5.6	30	33.3
Pharynx (also lip and tongue)	47	7	14.9	17	36.2	—	—	—	—	—	—	1	2.1	22	46.8
Prostate	19	1	5.3	2	10.5	12	63.2	—	—	—	—	2	10.5	2	10.5
Skin, face	20	5	25.0	7	35.0	1	5.0	1	5.0	—	—	—	—	6	30.0
Stomach	42	19	45.2	4	9.5	1	2.4	10	23.8	—	—	—	—	8	19.1

TABLE 3.—DISTRIBUTION BY LOCATION OF CARCINOMAS IN CASES OF DEATH FROM ASCERTAINED IMMEDIATE CAUSES.

	Total number.	Bladder.		Prostate.		Breast.		Uterus (cervix).		Uterus (fundus).		Skin (face).		Pharynx, lip, tongue.		Esophagus.		Stomach.		Rectum and colon.		Other organs.	
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Cachexia	114	1	0.9	1	0.9	29	25.4	10	8.8	2	1.8	5	4.4	7	6.1	3	2.6	19	16.7	20	17.5	17	14.9
Pneumonia	70	2	2.9	2	2.9	10	14.3	6	8.6	—	—	7	10.0	17	24.3	4	5.7	4	5.7	13	18.6	5	7.1
Pulmonary insufficiency	25	—	—	—	—	19	76.0	1	4.0	—	—	—	—	—	—	—	—	—	—	—	—	5	20.0
Pulmonary embolus	24	1	4.2	2	8.3	3	12.5	3	12.5	2	8.3	—	—	1	4.2	1	4.2	—	—	5	20.8	6	25.0
Peritonitis	56	1	1.8	—	—	3	5.4	9	16.1	5	8.9	1	1.8	—	—	1	1.8	10	17.9	21	37.5	5	8.9
Renal insufficiency	65	17	26.2	12	18.5	2	3.1	27	41.5	2	3.1	1	1.5	—	—	—	—	1	1.5	1	1.5	2	3.1
Hemorrhage	20	—	—	—	—	—	—	1	5.0	2	10.0	2	10.0	6	30.0	—	—	1	5.0	—	—	8	40.0
Hepatic insufficiency	20	—	—	—	—	6	30.0	1	5.0	—	—	—	—	—	—	—	—	1	5.0	5	25.0	7	35.0
Intestinal obstruction	20	—	—	—	—	2	10.0	2	10.0	1	5.0	—	—	—	—	—	—	—	—	12	60.0	3	15.0
Other causes	86	1	1.2	2	2.3	13	15.1	4	4.7	1	1.2	4	4.7	16	18.6	8	9.3	6	7.0	13	15.1	18	20.9

In the deaths from renal insufficiency (13 per cent of the total) are included those cases which died with definite signs or symptoms of uremia, and where at autopsy there was found hydronephrosis, pyonephrosis, pyelonephritis or multiple abscesses of the kidneys. The very few cases of true nephritis encountered in this series are included under the heading "Cardiorenal." By far the greatest number of deaths from renal insufficiency are caused by carcinoma of the cervix uteri, 41.5 per cent. Carcinoma of the bladder accounted for 26.2 per cent and carcinoma of the prostate 18.5 per cent.

Ureteral obstruction in cases of carcinoma of the cervix is usually low, due either to infiltration of the tumor process into the tissues of the posterior bladder wall and about the lower ends of the ureters, or else to compression of the ureters by iliac lymph nodes enlarged through the metastasis of tumor to them. Occasionally postradiation fibrosis results in obstruction. In the cases of carcinoma of the bladder the obstruction again is usually due to infiltration of the bladder wall, obstructing the ureteral orifices. On the other hand, carcinoma of the prostate produces obstruction at the urethral orifice just as benign hypertrophy of the gland. In contrast to the large number of cases of carcinoma of the cervix producing urinary obstruction, this was present in less than one-seventh of the cases of carcinoma of the fundus uteri.

Peritonitis, occurring most frequently as a postoperative complication or as the result of postradiation necrosis and perforation, but occasionally as the result of direct extension of the tumor, accounted for 56 or 11.2 per cent of the fatalities.

Under the heading "Pulmonary Insufficiency" are included those cases where the immediate cause of death was sufficient destruction of the lung parenchyma by the tumor to produce asphyxia, compression of the lung by pleural exudate secondary to tumor metastases, or massive collapse of the lung. This group of causes contributed 5 per cent of the fatal cases. A closely related cause falling just short of 5 per cent of the total deaths is embolism of the pulmonary artery or embolism to the right heart. Seventy-six per cent of the cases of pulmonary insufficiency are due to the metastases from carcinoma of the breast.

If we lump together the various fatal lesions affecting the lung, that is, pneumonia, pulmonary insufficiency, abscess of the lung and pulmonary embolism, the group assumes even greater numerical importance than cachexia.

Hemorrhage accounts for an extraordinarily small number of the deaths from carcinoma, only 4 per cent in this series. In one-fourth of the cases of hemorrhage the carcinoma is the indirect cause only, since the presence of the tumor had produced a high degree of obstructive jaundice, the underlying cause of the fatal hemorrhage.

In 14 cases it was impossible to establish the immediate cause of death.

TABLE 4.—THE CAUSES OF DEATH BY ORGANS IN 500 CASES OF CARCINOMA.

	Abscess, lung.	Cachexia.	Embolism, heart and lung.	Endocarditis.	Hemorrhage.	Hemorrhage (cerebral).	Hepatic insufficiency.	Intestinal obstruction.	Intracranial pressure.	Cardiorenal.	Peritonitis.	Pneumonia.	Postoperative collapse.	Pulmonary insufficiency.	Renal insufficiency.	Sepsis.	Starvation.	Thrombosis.	Tracheal obstruction.	Not stated.	Total.
Adrenal	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1
Bladder	—	1	1	—	—	—	—	—	—	—	1	2	1	—	17	—	—	—	—	—	23
Breast	—	29	3	—	—	2	6	2	2	1	3	10	2	19	2	2	—	—	1	3	87
Cecum and colon	—	5	1	—	—	—	3	5	—	—	8	4	—	—	—	1	—	—	—	—	27
Cervix	—	10	3	—	1	—	1	2	—	—	9	6	—	1	27	4	—	—	—	—	64
Esophagus	5	3	1	—	—	—	—	—	—	—	1	4	2	—	—	—	1	—	—	—	17
Kidney	—	3	1	—	—	—	—	—	—	—	—	—	—	1	1	1	—	—	—	2	9
Larynx	2	2	—	—	—	—	—	—	—	—	—	3	—	—	—	—	—	1	—	1	9
Lip	1	1	—	—	1	—	—	—	—	—	—	2	—	—	—	—	—	—	—	—	5
Liver and ducts	—	2	—	2	3	—	4	—	—	—	1	—	—	1	—	—	—	—	—	—	13
Ovary	—	4	—	—	—	—	1	3	—	—	3	—	—	1	1	—	—	—	—	—	13
Pancreas	—	2	2	—	2	—	1	—	—	1	—	2	—	1	—	—	—	—	—	3	14
Pharynx and antrum	4	5	1	—	2	—	—	—	—	—	—	8	—	—	—	3	—	1	—	1	25
Prostate	—	1	2	—	—	—	—	—	—	1	—	2	—	—	12	—	—	1	—	—	19
Rectum and sigmoid	—	15	4	—	1	—	2	7	—	—	13	9	3	—	1	7	—	2	—	—	63
Salivary gland	—	—	1	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	2
Skin (face)	—	5	—	—	2	—	—	—	1	—	1	7	—	—	1	2	—	—	—	1	20
Skin (body)	—	2	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3
Stomach	—	19	—	—	1	—	1	—	—	—	10	4	3	—	1	1	—	1	—	1	42
Testis	—	2	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	1	4
Tongue	4	1	—	—	3	—	—	—	—	—	—	7	—	—	—	—	1	—	—	1	17
Uterus	—	2	2	—	2	—	—	1	—	—	5	—	—	—	2	1	—	—	—	—	15
Vulva (vagina)	—	—	1	—	1	1	1	—	—	—	1	—	—	1	—	1	—	1	—	—	8
Total	16	114	24	2	20	3	20	20	3	3	56	70	11	25	65	24	2	7	1	14	500

Although one would expect the resistance of these debilitated patients to be greatly lowered and although extensive secondary infection is often present in the tumors, sepsis *per se* is an extraordinarily infrequent cause of death, amounting to less than 5 per cent.

One rather striking group of cases, though small, is that which we may call hepatic insufficiency. This group is characterized by jaundice of obstructive type, usually painless, and anorexia, nausea. At autopsy the liver may be much enlarged (4000 to 6000 gm.) but hardly more than 200 to 300 gm. of liver substance remain between the metastatic nodules.

Summary and Conclusions. 1. The immediate cause of death has been studied in 500 cases of carcinoma.

2. Cachexia is the most frequent single cause, although exceeded by the total of the various pulmonary disorders.

3. Cachexia is associated most frequently with cancer of the breast, stomach and large bowel.

4. By far the commonest cause of death in carcinoma of the cervix uteri is renal insufficiency.

5. Sepsis is an unimportant factor in fatal cases.

6. The striking association of carcinoma of the buccal mucosa with pneumonia (36.2 per cent) and with lung abscess (56.3 per cent) emphasizes the rôle of aspiration in the production of these lesions.

OXYGEN THERAPY—A CRITICAL RÉSUMÉ.

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Any therapeutic advance must go through a probation period either under controlled conditions in the laboratory or in the longer, harder school of everyday trial. Oxygen therapy has been going through this period. It is the purpose of this paper to attempt to give a résumé of the status of oxygen therapy after a rather intense 10-year probation period.

The Purpose of Oxygen Therapy. The primary purpose of oxygen therapy is the combating of anoxemia, the clinical importance of which has been recognized since Haldane's monumental book, "Respiration" (1922).[1] Knowledge of various aspects of general metabolism has advanced with astonishing rapidity. Rarely, however, is the oxygen content of the blood of routine concern in the minds of most. The reasons for this apparent neglect are, first, that our knowledge of anoxemia is relatively newly acquired and certainly complex; second, that the method of determining the oxygen saturation of the blood needs simplification. Facilities for the determination of the degree of anoxemia are not to be found in the ordinary clinical laboratory, but the time will come, I venture, when the degree of anoxemia in certain diseases will be considered as regularly as the leukocyte count now is in acute appendicitis.

Difficulties in Applying the Statistical Method to an Evaluation of Oxygen Therapy. One of the most frequent arguments used against oxygen therapy is the absence of statistics showing a decrease in the death rate of treated patients, as compared with untreated patients. Mature consideration, however, demonstrates the difficulties in acquiring such statistics. For instance, up to the present time only the severest cases have been selected for treatment. Furthermore, there are too many complex factors which influence the mortality in pneumonia, such as the type of organism, the age of the patient and the presence of bacillemia, to make it feasible by the statistical method to assign accurately the relative importance of oxygen in this complex group of factors. Oxygen therapy should not be looked upon as a specific measure in pneumonia, for example, any more than we look upon the use of glucose as a specific measure. That glucose is frequently of assistance in the treatment of pneumonia no one questions. Oxygen should be similarly regarded and should receive greater emphasis, if anything, as there is no mechanism in the body for the storage of oxygen.

Terminology. An appreciation of the following definitions is essential to an understanding of the literature on the subject. By procuring samples of arterial[2] and of venous[3,4] blood, procedures attended by little if any risk, it is possible by the usual gasometric technique[5] to determine the oxygen content. A portion of the blood is then saturated with oxygen and the total oxygen capacity is determined. Thus are obtained (1) arterial oxygen content (cubic centimeters of oxygen combined with hemoglobin per 100 cc. of arterial blood); (2) venous oxygen content (a similar value for venous blood); (3) total oxygen capacity (cubic centimeters of oxygen combined with the hemoglobin of 100 cc. of blood when fully saturated).

The difference between the oxygen content and total oxygen capacity has been named by Lundsgaard[3] the oxygen unsaturation. This term can be used in speaking of either arterial or venous blood. The unsaturation may be expressed either as cubic centimeters of oxygen per 100 cc. of blood or as percentage of the total oxygen capacity. In the latter the data represent the per cent of total hemoglobin in the form of reduced hemoglobin. The oxygen consumption is the difference between the arterial and venous oxygen content.

Only approximate figures can be given for these factors. An example will make this clear:

	Cubic centimeters.	Per cent.
Arterial oxygen content	18	90 (av. 95)
Venous oxygen content	14	70
Total oxygen capacity	20	100
Arterial oxygen unsaturation	2	10
Venous oxygen unsaturation	6	30
Oxygen consumption	4 (2.6 to 8.3)	20

It is apparent that these terms fail to take into consideration the oxygen tension in the tissues, a factor of the utmost importance. No feasible method is as yet available to render such information accessible. In this very important particular is our knowledge of anoxemia seriously lacking, for surely the justification for the existence of the elaborate mechanisms for absorption and transportation of oxygen is its utilization in the tissues. We must be content at present with a study of the per cent saturation of the arterial and venous blood.

From the studies of Binger,[6] Stadie,[7] Harrop,[8] Pilcher and Harrison,[9] and others, our knowledge concerning the degree of anoxemia occurring in many conditions is rapidly growing. Some of these will be referred to later.

Cyanosis is the Clinical Test for Anoxemia. While it must be conceded that anoxemia and cyanosis, strictly speaking, are not synonymous terms, still for practical purposes we are obliged at present to rely on the degree of cyanosis as an index of anoxemia

and, indeed, for our indications for oxygen therapy. The relationship between these two conditions is well presented by Peters and Van Slyke.[10] They state, "In conditions such as pneumonia, where both cyanosis and tissue anoxia are caused primarily by incomplete oxygenation of the arterial blood, while hemoglobin content is normal and the onset is too rapid for much tissue adaptation to oxygen deficit, there may be a close parallelism between cyanosis and anoxemic symptoms."

Stadie[4] has given careful consideration to this subject and finds a definite relationship in pneumonia between the degree of cyanosis and the per cent of arterial unsaturation. With increasing cyanosis the arterial unsaturation becomes greater. The venous unsaturation varies similarly. The following table shows this relationship:

ARTERIAL AND VENOUS OXYGEN UNSATURATION ASSOCIATED WITH CYANOSIS OF VARYING DEGREE.

Cyanosis.	No. of observations.	Unsaturation, per cent.	
		Mean arterial.	Mean venous.
None	18	5.8	23.8
Slight	11	11.8	30.4
Moderate	10	17.2	41.8
Marked	13	26.0	51.2
Intense	4	53.2	82.3

The distribution of the cyanosis is of interest in that the most constant and frequent site was found to be in the end of the finger, especially under the nail. As it became more intense it could next be observed over the entire end of the finger, being more marked on the dorsal aspect. Next to the finger the face showed cyanosis most commonly. Marked hourly variation in this location was common, however, thus making the nail the most constant guide. The importance of avoiding the development of cyanosis, if possible, cannot be overemphasized. Certain irreparable toxic changes are known to occur in vital neural cells in the presence of anoxemia, as has been shown by Cannon[11,12] and his coworkers, and these may be prevented by the early use of oxygen.

General Symptoms of Anoxemia. When anoxemia is of very rapid onset, loss of consciousness may occur without any warning, as when a miner puts his head into a cavity full of methane gas and drops as though felled by a blow. When he recovers, on breathing pure fresh air for a minute, he really feels that he has been knocked down and acts accordingly, assaulting any one in the vicinity. If anoxemia develops more gradually, the intellect and the senses become dulled without the person being subjectively aware of what has happened. When the anoxemia is relieved the sudden increase in power or in visual acuity comes as a great surprise.

Symptoms similar to those resulting from an overdose of alcohol may be present, such as headache, depression, apathy and drowsiness; or excitement and general loss of self-control. The subject

will sing or shout or burst into tears for no apparent reason. He may be extremely quarrelsome or insolent. Indeed, Palthé[13] has shown that the symptoms of acute alcoholism, both in animals and men, may be completely suppressed by the breathing of pure oxygen, only to return again, however, as soon as the oxygen is removed.

Understanding is impaired more than sensation. Pain is dulled. Finally, each sense is lost, hearing being retained longest. (This fact suggests the exercise of more circumspection in our remarks at the bedside of a presumably delirious patient.) The subject misjudges the position of things and cannot walk straight. There is great muscular weakness and easy fatigability. We are accustomed to attribute the astonishing delirium so frequently seen in pneumonia largely to the fever and toxemia. As a possible anoxemic symptom this delirium appears in a new guise. Much of the behavior of a delirious pneumonia patient finds an exact counterpart in anoxemia experimentally produced in man and dogs (Greene and Gilbert[14]).

Another and often still more serious danger arises from the gradual and insensible failure of judgment. A man suffering from anoxemia will usually insist on going on with what he set out to do. An aviator continues to ascend oblivious of danger; a miner engaged in rescue or exploration work, or in dealing with an underground fire, insists on going on when he is suffering from the anoxemia of CO poisoning and often fights any one who tries to make him desist. Recent ventures into the stratosphere, together with the exuberant growth of aviation, are affording opportunities for very practical utilization of this fund of knowledge.

Delayed Symptoms of Anoxemia. Besides the immediate symptoms there are a number of delayed symptoms or after-effects. These depend partly on the length and partly on the severity of the exposure. One of Haldane's acquaintances has twice knocked down persons on waking up from a short loss of consciousness caused by anoxemia. The best known delayed effect of slight anoxemia is the so-called mountain sickness. A stay of several hours is required to cause this sickness, which usually is felt 8 to 12 hours after the beginning of the exposure. Similarly, a percentage of carbon monoxid, which produces no immediate noticeable effect will, with sufficiently long exposure, cause headache and nausea. At present we can only conjecture as to the nature of the slight temporary pathologic changes of which mountain sickness symptoms are the manifestations.

Adaptation or Acclimatization in Anoxemia. Adaptation or acclimatization may act in two different ways. As Haldane[1] says, "Adaptation may bring it about that the anoxemia which would, without adaptation, exist, is greatly diminished. This form of adaptation is very clearly seen in persons living at great altitudes. In the second place, the tissues may adapt themselves to a lower partial pressure of oxygen. About this second form of adaptation

our knowledge is at present very imperfect; but it seems that clinical evidence points strongly to its existence. Perhaps the clearest evidence is afforded by cases of congenital heart defect. The remarkable point is that in spite of the anoxemic condition of the blood, these people may get on quite well and be able to walk at a good pace. On account of the large increase in the quantity of hemoglobin they have plenty of oxygen in their blood, but at a low partial pressure. It hardly seems possible to doubt, therefore, that their tissues have become adapted to the low partial pressure of oxygen." The fact that anoxemia may exist without harm in chronic cases of disease has certainly contributed to the general failure to recognize the gravity of anoxemia in persons not adapted. Greater knowledge concerning this form of adaptation may conceivably revolutionize our existing ideas regarding anoxemia.

Physiology of Oxygen Therapy. Under normal conditions an individual in bed requires for the maintenance of his metabolism from 15 to 18 cc. of oxygen per breath. Only 21 per cent of the inspired air is oxygen, and since the ordinary tidal air is about 500 cc., this means only about one-fifth of the available oxygen is used. On first thought this appears to be a generous reserve, and indeed is, which Nature has provided for this vital function. In diseased states, however, especially in the presence of fever, the oxygen requirement of the tissues mounts rapidly. Add to this the crippling effect of a marked reduction in the vital capacity of the lungs, as, for example, by a large area of consolidation with its associated edema and inflammatory reaction. An increased pulse rate can partially compensate by hastening the red cells around at a more rapid rate. An increase in the oxygen capacity of the blood also helps.[7] Gradually oxygen unsaturation increases. The available oxygen in the inspired air remains constant. The respiratory rate increases with its accompanying fatigue, but the amount of air taken in per breath is limited by the vital capacity. The more rapid the respirations the shallower they must be. Hence, the most logical method of breaking this vicious circle would be by increasing the oxygen concentration in the inspired air and, thus, the available oxygen per unit of air.

Mechanisms of Anoxemia in Pneumonia. Consideration of the actual mode of production of anoxemia in pneumonia has brought to light a number of factors, each one of which very probably plays a part. It is apparent that the trouble may be found in either the pulmonary ventilation, the alveolus, the circulating blood or the tissues. Inadequate oxygenation, accordingly, may be due to the following:

1. Failure of adequate ventilation, due simply to rapid, shallow breathing.

2. Some intrinsic alveolar disturbance, due to such factors as: (*a*) the mechanical interference by intraälveolar exudate of such

quantity as to prevent access of air, which with intact circulation allows unaërated blood to return to the systemic circulation; (*b*) dysfunction of alveolar membranes due to edema and faulty nutrition; (*c*) interference with circulation in alveolar walls, brought about by formation of fibrin plugs within the capillaries. If this interference were extensive enough, either with or without normal alveolar capacity, this would tend to hasten the blood flow through the remaining vascular channels, thereby shortening the duration of contact between blood and air.

3. The intrinsic changes in the circulating blood due to changes in the behavior of hemoglobin with the formation, for example, of methemoglobin.

4. Intrinsic tissue disturbance.

1. Failure of Adequate Ventilation Due Simply to Rapid, Shallow Breathing. Meakins,[15] in 1920, stated that, "Anoxemia occurring in acute lobar pneumonia is a result of the rapid, shallow breathing typical of this condition, which breathing at times scarcely gets air past the dead space in the trachea." Stadie,[7] however, after careful consideration of this question, concluded on the basis of quantitative considerations that appear irrefutable that the degree of tachypnea observed in any of his cases was incapable of itself of producing anoxemia of the extent encountered. Binger and Davis,[16] out of 16 anoxic pneumonia patients, observed only one in whom the respiration was so shallow (127 cc. tidal air) that a major rôle in producing the anoxia could be assigned to the type of respiration.

2. Intrinsic Alveolar Disturbance. (*a*) *Mechanical Interference by Intraälveolar Exudate.* Stadie[7] first pointed out that "as a rule, when the pneumonia process is confined to one area, as in the typical lobar pneumonia variety, there is little or no cyanosis. The physical signs, *viz.*, dullness, bronchial breathing and a few fine râles, are then confined to the area involved. Kline and Winternitz,[17] and later Gross,[18] have shown that in this type of consolidation there is little or no circulation of blood to the consolidated lung, and therefore little or no admixture of nonaërated with aërated blood occurs. When, however, there is a spread of the pneumonic process and there occur scattered and secondary areas of bronchopneumonia, the blood circulation in these areas is intact. Moreover, there is a more or less widespread bronchitis with peribronchial pneumonia and edema. The lung signs are changed . . . and anoxemia results." Many of the alveoli are functionless due either to occlusion of the bronchioles or to interference by intraälveolar exudate, with the result that unaërated blood is allowed to return to the circulation, thereby augmenting the anoxemia.

(*b*) *The Dysfunction of Alveolar Membranes Due to Edema, Faulty Nutrition or Interference by a Plastic Exudate.* Barach[19] has called attention to the fact that in those conditions in which there is a

formation of pulmonary exudate or transudate, the presence of this material interferes with the gaseous exchange through the alveolar wall. This factor makes itself felt more especially in the areas of pneumonitis surrounding larger areas of consolidation.

(*c*) *Interference with Circulation in the Alveolar Walls.* Kline and Winternitz[17] have shown that in the areas of gray hepatization there is little or no circulation of blood due to the formation of fibrin plugs within the capillaries, so-called fibrin capillary thrombi. With or without adequate alveolar capacity, if this vascular disturbance were extensive enough it would tend to hasten the blood flow through the remaining vascular channels, thereby shortening the duration of contact between blood and air, and decreasing the degree of oxygenation. Binger, Brow and Branch[20] have recently elaborated this point. Greene[21] points out, however, that "the blood in the normal lung is in the pulmonary capillaries only about 1 second, yet the oxygen diffuses through into the venous blood fast enough to oxygenate it to arterial blood within the first two-fifths of this time. There is a variation among individuals, but a 60 per cent margin of safety in diffusion time exists. . . . In pulmonary inflammation, on the other hand, especially when associated with edema, the rate of absorption of oxygen may be greatly reduced." So that with an accelerated rate of blood flow in the presence of edema of the alveolar membranes, it is quite likely that this factor may contribute appreciably to the degree of anoxemia.

3. Intrinsic Changes in the Circulating Blood. Peabody, in 1913,[22] attempted to show that the terminal symptoms and death in pneumonia are in part dependent on the changes produced in the hemoglobin molecule by the growth of the pneumococcus. This observation was based on experiments *in vitro*[23] which showed that the growth of pneumococcus on blood decreases the capacity of the blood for combining with oxygen. Further confirmation[24] was found in the changes of the blood of animals suffering with severe pneumococcus bacteremia, which changes were due to the conversion of hemoglobin into methemoglobin. Peabody[22] then studied the blood of patients suffering from pneumonia and stated that "in the human body and in experimental animals death occurs before enough methemoglobin has been formed to be visible spectroscopically, but the falling off of the oxygen-combining power of the blood indicates that such a change is taking place." He was never able to demonstrate methemoglobin spectroscopically, however, and concludes that "while not attempting to assign a rôle that is all important to the changes in the blood, it would seem correct to consider that in many cases of pneumonia the terminal symptoms and death are in part produced in the hemoglobin molecule by the growth of the pneumococcus." It is not possible, therefore, at present to be able to assign a very considerable rôle to intrinsic changes in the blood in the production of anoxemia in pneumonia.

4. Intrinsic Tissue Disturbance. There is little evidence in the literature upon which to base the belief that some intrinsic tissue disturbance is responsible to any considerable extent for the anoxemia of pneumonia. Stadie[7] discusses the oxygen tension of the blood and tissue tension and gives a careful review of the available literature. About all that can be said is that the relations between normal and anoxic tissue function are not definitely established.

It might be argued that the existence of anoxemia in the course of pneumonia is of value in initiating certain defense reactions of the body in much the same way as fever is thought to do. In some ways such a position is not untenable in that, as Strughold[25] has recently shown, anoxemia in milder degrees leads to an increase in the minute volume flow of blood which effect would be distinctly beneficial to the pneumonic lung where the acute problem lies in furnishing adequate oxygen to the blood and in turn to the tissues. By increasing the minute volume flow a larger amount of oxygen, assuming adequate oxygen diffusion in the alveoli, would be delivered to the tissues. Serious complications arise in more advanced anoxemia, however, as shown by Schneider and Truesdell,[26] when there occurs a definite decrease in the minute volume of flow associated as a rule with dilatation of the heart. This early stimulating effect and later depressant action is apparently a direct action on the heart. As previously pointed out, Cannon and his coworkers[11,12] have demonstrated the susceptibility of the cells in the vital brain centers to anoxemia.

It should be added that while all these various mechanisms probably play a part in the production of anoxemia in pneumonia, it appears certain that the chief causes, as pointed out by Peters and Van Slyke,[10] are those related to the anatomic changes which retard the access of oxygen to the pulmonary blood.

Is There Danger of Overdosage of Oxygen? A careful discussion of this question involves the review of an extensive literature. Rather painstaking experimental work has been done on both man and animals but, unfortunately, considerable misinformation has arisen from it. In the first place, the older literature deals with work done on small laboratory animals, from which accurate conclusions cannot be drawn for man. As all of the work reported, furthermore, has been done on the normal organism, conclusions cannot be applied to the abnormal.

Smith, in 1899,[27] first discovered the poisonous effects of too much oxygen. He observed fatal pneumonia in rabbits exposed to over 80 per cent oxygen for 2 to 4 days. Benedict and Higgins,[28] in 1911, considered this question and give an excellent review of the literature. Man was used as the subject but the exposures to oxygen-rich mixtures were only of 10 or 15 minutes' duration. Karsner,[29] in 1915, further reviewed the literature and concluded,

from work done on rabbits, that atmospheres containing 80 to 96 per cent oxygen under normal barometric pressure produce in 1 or 2 days congestion, edema and, finally, a fibrinous bronchopneumonia. Barach,[30] in 1926, and Binger[31] and his associates, more recently, confirmed these findings in rabbits. These conclusions, perhaps unconsciously, have been applied directly to man. It must be remembered, however, that blood fully saturated with oxygen cannot be expected to respond the same as blood markedly unsaturated; nor can abnormal alveolar membranes be expected to respond to oxygen as do normal ones.

The extensive literature on oxygen therapy contains no convincing evidence that any harmful effects attributable to oxygen itself have ever come from even continuous exposure of anoxemic or potentially anoxemic individuals to atmospheres of from 40 to 60 per cent oxygen for periods of as long as 2 months. This is a conservative statement to which there is only one exception, namely, conditions of chronic anoxemia as in chronic pulmonary disease and congenital heart disease where the factor of acclimatization has entered. These cases must be selected with care, as Boothby and Haines[32] point out, for once they are in oxygen tents they frequently cannot be removed without causing an attack of acute "mountain sickness" which, in the debilitated condition in which these patients often are, proves fatal.

Indeed, there is a growing feeling that the administration of pure oxygen has definite advantages. Evans[33] has recently given a discussion of this subject from an experience arising from the administration of pure oxygen by means of a face mask to more than 100 cyanotic patients, for periods varying from 1 to 27 days, the administration being as nearly continuous as possible. He reports entirely satisfactory results with the development of no symptoms that might be attributed to an irritative action of the oxygen.

Actually the longest we have kept a patient under an oxygen tent practically continuously with resulting recovery is 22 days. The patient's pneumonia was complicated by bilateral empyema. Barach[34] reports having kept a patient, suffering with active bilateral pulmonary tuberculosis, under a tent for 7 months, with no evidence of irritation from the oxygen.

Dosage. At present it is felt that the optimum concentration of oxygen is between 40 and 60 per cent.[35] Any method which can supply a concentration above 30 per cent continuously and comfortably is of value. An oxygen concentration of less than 30 per cent rarely has any value; 30 to 35 per cent oxygen concentration generally lessens cyanosis and increases the arterial oxygen saturation. The nasal catheter method which is universally available will, when properly employed, furnish up to 35 per cent.[38] Its use should be continuous—day and night—if this be necessary to keep the patient comfortable. "Keep the finger nails pink," is a criterion

described by one clinician.[36] This is excellent but presupposes that cyanosis has developed. Stadie[4] has shown that cyanosis of the finger nails and lips that just can be detected corresponds to approximately 10 per cent oxygen unsaturation. When cyanosis is definite the blood will be approximately 15 per cent unsaturated, and when marked, 20 to 30 per cent. Wineland and Waters[37] have recently attributed great importance to the pulse rate, this being, they assert, the most reliable single guide by which to judge benefit or failure from oxygen therapy. This point finds further confirmation in the work previously mentioned of Benedict and Higgins,[28] who found the lowering of the pulse rate to be the only factor in the metabolism of normal man, which shows consistent change in exposures to oxygen-rich atmospheres. In normal man the higher the percentage of oxygen breathed (up to 90 per cent), the lower the pulse. The fever may be uninfluenced because of the toxicity of the organism. The slowing of the pulse, however, occurs commonly, and is an indication that the part of the rapidity of the pulse due to the anoxemia is being relieved. Attention to the pulse, then, often is our best index. Our plan is to err on the side of safety and during the height of an infection, where experience has shown anoxemia is a factor, the patient is kept under the oxygen tent.

Indications for Oxygen Therapy. Medical Conditions. *Pneumonia.* Oxygen therapy is indicated in both lobar and bronchopneumonia. That oxygen unsaturation exists in pneumonia has been proven beyond doubt.[4,6,8,44] That this unsaturation can be overcome by oxygen therapy has also been shown conclusively, both clinically as well as with confirmatory blood gas studies.[7,19,39] The mass of reports in the literature from various workers all are in favor of early and continuous use of oxygen. The following statements summarize the effects of oxygen therapy in pneumonia which have been observed: (1) it gives greater comfort by making breathing easier; (2) it slows the pulse and, at times, the respiration and often lowers the temperature; (3) it increases the arterial oxygen saturation and relieves cyanosis; (4) finally, it frequently prolongs life until such time as the immunity mechanism is able to achieve recovery.

Even though precise statistical proof of the value of oxygen therapy is still lacking, these benefits cannot be ignored.

The first complete study of arterial and venous oxygen in pneumonia was made by Stadie[4] in 1919. His contribution has been significant in that it has furnished a firm scientific foundation, now amply verified, for much of the speculation concerning oxygen therapy. He demonstrated that in all cyanotic pneumonia patients the blood was incompletely oxygenated. Furthermore, cases without cyanosis have an arterial unsaturation close to normal, which fact indicates that in pneumonia cyanosis is a reliable indication of the degree of anoxemia present. He showed that the anoxemia

of cyanotic pneumonia patients was entirely of the arterial or anoxic type and due to incomplete saturation of venous blood with oxygen in the lungs. It was not due to stagnation as the difference between the arterial and venous oxygen content, *i. e.*, oxygen consumption, was quite normal (3 to 5 volumes per cent).

A close correlation also was shown to exist between arterial unsaturation and mortality. In the fatal, as opposed to the non-fatal cases, the mean arterial and venous oxygen unsaturation respectively was 32 and 57 per cent, as against 13.9 and 36.3 per cent. Oxygen unsaturation of over 20 per cent as a rule was associated with a fatal outcome.

Binger[6] has investigated more recently the correlation between anoxemia and mortality. His study calls attention to the comparatively few figures which have been published concerning the degree of arterial oxygen unsaturation which occurs in pneumonia, or the changes in saturation which follow oxygen therapy. His study presents the results of over 300 arterial punctures, and oxygen analyses made in 137 patients. By means of a simple frequency table he studied the percentage distribution of the various grades of anoxemia. There appeared to be a positive correlation between anoxemia and mortality. Moreover, the level of oxygen saturation in the arterial blood of a patient exposed to 40 per cent oxygen is of prognostic importance since the survivors usually reach a level of 90 per cent, while the fatal cases do so far less often. This is the first careful study presenting information obtained after exposures to oxygen-rich atmospheres that has appeared, and its value is vitiated by the size of the series studies.

It must be said, as Stadie[7] points out, that not until the relation of function to oxygen tension is further elaborated can it be definitely said that anoxemia *per se* is a factor in the fatal outcome. It is fairly certain that a high degree of anoxemia in pneumonia is accompanied by a high mortality.

Heart Disease. *Cardiac Decompensation.* The indications for the use of oxygen therapy in heart disease are by no means clear. Many instances of its empirical use can be found, but not until recently has any intelligent concerted effort been made to study the problem clinically. Physiologists long ago uncovered many of the fundamental facts, but their clinical utilization, unfortunately, has been beset with grave difficulties. The complexity of cardio-respiratory physiology is apparent and even in the normal organism with the variation of one factor there occurs an elaborate shift in many others. These readjustments are further complicated by the presence of disease.

In heart disease the problem of the intelligent use of oxygen therapeutically is complicated by the fact that all three major types of anoxemia occur, and at times in the same patient. In pneumonia the contrast is apparent, as here anoxic anoxemia is

the major problem. The occurrence of anoxic anoxemia in heart failure was demonstrated first by Harrop[8] and amply confirmed by Barach and Woodwell,[19] Campbell, Hunt and Poulton,[41] Rabinowitch,[42] and others. That stagnant anoxemia occurs has also been proved by Means and Newburgh,[43] Lundsgaard,[44] Harrop,[8] and Barach and Woodwell,[40] among others. The occurrence of anemic anoxemia in such heart conditions as subacute bacterial endocarditis and hypertension associated with chronic glomerulonephritis needs no elaboration.

It is encouraging that from efforts chiefly of Barach[45] and his associates[46] and Hamburger, *et al.*,[47] the clinical phases of this problem are being clarified. Barach[46] states, "The most interesting and striking effects of oxygen therapy in the cases of cardiac insufficiency, both those due to local disease of the heart itself and those in which heart failure appeared to be secondary to primary pulmonary disease, are: (1) relief of dyspnea and orthopnea; (2) elevation of the arterial carbon dioxid content and of the level of the carbon dioxid dissociation curves, and (3) diuresis."

In discussing the physiology of these effects Barach[46] says, "(1) The relief of dyspnea which frequently manifests itself within several hours after removal to oxygen-rich atmosphere indicates that oxygen want plays a decisive rôle in the production of cardiac dyspnea. It is evident (1) that the difficulties in oxygen absorption resulting from lung stiffening, decreased vital capacity and swollen alveolar membranes were overcome and (2) that the increased oxygen saturation of the pulmonary blood tends to diminish tissue acid accumulation. In the one case measured, the blood lactic acid rapidly returned to normal (22.6 mg. to 7 mg.). That the respiratory stimulus was thereby decreased is evidenced by the lowered pulmonary ventilation and that there was some decrease in general tissue acidity was suggested by the small but constant lowering of the arterial hydrogen-ion concentration which we observed."

In discussing the elevation of the arterial carbon dioxid content Barach[46] states, "When the anoxemia is relieved, there is a constant and marked rise in the carbon dioxid concentration of the blood with an even greater elimination of carbon dioxid per breath through the congested lung. Thus, in one of the cases of congestive failure, the carbon dioxid content of the arterial blood rose from 38.4 to 69.9 volumes per cent in 4 days. It appears, therefore, likely that the elevation in carbon dioxid level in the blood is an adaptive change which is readily accomplished if sufficient oxygen is supplied to maintain normal metabolic activity. Also, lactic acid accumulation disappears when anoxemia is relieved. It seems probable that base to retain carbon dioxid is in part derived from the blood lactates in this man. A decrease in pulmonary ventilation follows with a lessened sense of pulmonary effort, and therefore relief of dyspnea."

Knowledge concerning the mechanism of the diuresis which occurred is incomplete. Barach[46] merely states that, "oxygen therapy resulted in an improved state of the circulation which would tend to relieve the edema due to stasis as well as relieve the passively congested glomerular membranes. In so far as the tissue cells of the body are altered in their permeability due to anoxemia, an increased oxygen supply would otherwise be beneficial."

It would seem, therefore, in the presence of low arterial oxygen saturation, that while an old, damaged heart cannot be repaired fully by oxygen, nevertheless much of the acute distress so often seen in cardiac decompensation may be avoided to a large extent. During the time that digitalis, diuretics and morphin are taking to produce their effects it may be possible to put these patients in relative comfort by the use of oxygen.

Coronary Thrombosis. Levy and Barach[48] report their experience with the administration of oxygen by means of a tent to 4 patients suffering with coronary thrombosis. They state that their experience would indicate that anoxemia may play a crucial rôle in determining the outcome after coronary thrombosis. There is first of all a state of shock due to a sudden interference with the blood supply of the heart. If the resulting area of myocardial infarction is large, evidence of congestive heart failure swiftly ensues. The heart action becomes weak, sometimes irregular and rapid, with the characteristic muffling and shortening of the mitral first sound. The blood pressure falls sharply. Cyanosis appears and moist râles are heard at the base of the lungs. The breathing is rapid and difficult. Acute oxygen want is present, manifested by both arterial and venous anoxemia. Employment of oxygen therapy in a concentration of from 40 to 60 per cent may and has aided in maintaining an adequate oxygen supply to the tissues of the body until the heart has had an opportunity to recover from its acute functional disturbance.

In the experience of Barach there are cases in which the administration of oxygen will prolong life and result in recovery from the acute episode. Two out of 3 cases of coronary arteriosclerosis with chronic heart pain, reported by Barach,[49] have been relieved from exposures to an atmosphere of 50 per cent oxygen. These cases have been followed for approximately 6 months. Barach[46] states that it is not possible at present to explain entirely the mechanism by which the relief of the pain occurs. The following factors play a part. "In the first place, the inhalation of 50 per cent oxygen in normal men we have found capable of raising the arterial oxygen saturation from 95 to 99 per cent. In one of the cases of coronary arteriosclerosis, which we measured, the arterial oxygen saturation was raised from 94 to 99 per cent. Although this represents a small increase in per cent saturation, it indicates a considerable rise in the tension or partial pressure of oxygen available to the tissues

(because of the shape of the oxygen dissociation curve) and provides therefore a possible explanation for relief of local anoxemia in the heart muscles. The inhalation of high concentrations of oxygen causes the normal heart to beat at a slower rate,[28] and affects more markedly the heart in cardiac insufficiency, which suggests[40,50] a lessened strain due to a greater oxygen supply."

Oxygen Therapy in Allied Conditions. Less frequent is the indication for oxygen therapy in other medical conditions. Its use has been reported, however, in bronchitis[33,51] and asthma, hyperthyroidism,[52,53] asphyxia,[54] asphyxia of the newborn,[55,56,57,58] influenza,[33] and certain neuropsychiatric conditions.[49,59,60] Reports of the use of oxygen in other conditions such as epilepsy, chronic arthritis, sepsis, diabetes mellitus, burns and hypertension have appeared, but as yet conclusions cannot be drawn.

Surgical Conditions. The most interesting work in the use of oxygen in surgical conditions has perhaps been done in The Mayo Clinic (Judd and Passalacqua[61]). Boothby and Haines[62] early convinced this group of the advantages of oxygen therapy. Judd states that there are certain types of operations in which pulmonary complications are more likely to follow, such as interventions in the upper organs of digestion for cancer of the stomach, ulcer, gastrojejunal fistula, biliary obstruction and operations on the pancreas. Effort has been directed toward the development of some hygienic or therapeutic method that might minimize the possibility of postoperative pneumonia. It appears to them that since the use of the oxygen tent has been instituted they do not have in their service the incidence of pneumonia that they had at other times.

In this particular paper[61] 180 unselected cases are reported in which oxygen without CO_2 was administered under one of three sets of circumstances: (1) as a prophylactic measure against pneumonia immediately after operation; (2) as soon as the signs and symptoms of pulmonary congestion were recognized clinically; (3) after the classical signs of pneumonia were present. In the first group were 105 among whom pneumonia did not occur. The same results were evident in the second group of 43 with pulmonary congestion. In the third group not one casualty was registered and the progress of the disease apparently was influenced by the use of oxygen. It seems likely, however, that carbon dioxid will supplant oxygen to a large extent in the treatment of the postoperative pulmonary complications.

The Use of Carbon Dioxid With Oxygen in the Treatment of Pneumonia. Few topics are of more vital interest at present than the use of carbon dioxid in the treatment of pneumonia. Thoughtful workers with oxygen tents have frequently expressed the opinion that the absorption of carbon dioxid out of the system by the use of soda lime, aside from being expensive, was dangerous because it tended to remove the normal stimulant to respiration, and in

case of accidental obstruction of the oxygen tube would remove any possibility of warning. The recent trends toward elimination of soda lime[63] are efforts toward the elimination of these defects.

The function of carbon dioxid in the treatment of pneumonia has been elaborated most brilliantly by Y. Henderson and his coworkers, and many facts have been adduced which throw an entirely new light on our traditional ideas. Henderson[65] makes the interesting statement that "it is a significant fact that no one has yet reported the cure of an experimentally induced pneumonia by means of a vaccine, a serum or an antitoxin. On the other hand, experimental pneumococcic pneumonia has been cured with carbon dioxide." Their demonstration of the specific effect of carbon dioxid in preventing secondary pneumonia is fairly well known.[64] Now Henderson[65] feels that in all pneumonias by the use of carbogen, a convenient term for mixtures of oxygen and carbon dioxid, morphin, or other narcotic drugs may be used more freely to counteract excitement and restlessness. The stimulus to respiration afforded by the carbon dioxid tends to counteract the depression of breathing which such drugs otherwise induce. The value of morphin in pneumonia is established but individual experiences color our enthusiasms. In England there is a general belief that morphin affords fundamental and not merely symptomatic benefit in pneumonia. Henderson suggests the following rational explanation for this belief, "The principal physiologic effect of morphine . . . is to raise the threshold of the respiratory center for carbon dioxide. This means that respiration under morphine automatically decreases the volume of air breathed per minute to such an extent that, as the amount of carbon dioxide in the body is unaltered, a much higher concentration of carbon dioxide is maintained in the lungs even when there is no carbon dioxide in the inspired air. When, in addition, the patient breathes air containing an appreciable amount of carbon dioxide, the concentration increases to amounts corresponding to or somewhat exceeding those in the lungs during moderate physical exercise, but without its hyperpnea."

By means of this increase in the alveolar carbon dioxid content, the bactericidal action of carbonic acid upon the pneumococcus and the promotion of solution in the pneumonic exudate by carbonic acid may make itself felt. Lord[66,67] has called attention to these two probable actions of carbonic acid, but in order for these effects to be manifested carbon dioxid inhalation needs the assistance of morphin or some other respiratory depressant drug.

Kline and Winternitz[17] were able to show experimentally that "the presence of fibrin plugs throughout the capillary bed of the pneumonic lung interferes greatly with the penetration of such a diffusible substance as trypan blue, when this drug is injected intravenously, but the exudate offers no serious obstruction to the penetration of the dye into the alveoli when it is injected intrabronchi-

ally." This suggested to them a reason for the restricted action of immune serum in pneumonia, and further suggested a basis for the intrabronchial treatment of pneumonia. This is the approach which carbon dioxid therapy uses, and the soundness of it is further strengthened by these observations.

In conclusion, it can be seen that the interest in oxygen therapy has been of considerable magnitude during the past decade. It seems quite certain that oxygen therapy has definitely established itself in our therapeutic armamentarium. In those conditions associated with easily recognized anoxemia and in the more obscure conditions as they are recognized, the use of oxygen must find its place. Our knowledge must increase greatly before we can speak upon this subject with anything like finality. The time is at hand, however, when oxygen must be given a trial in serious heart and pulmonary conditions. That carbon dioxid will supplement oxygen seems possible, and a valuable supplement it bids fair to be.

BIBLIOGRAPHY.

1. Haldane, J. S.: Respiration, New Haven, Yale Univ. Press, 1922; London, Humphrey Milford, Oxford Univ. Press.
2. Hürtner: Deutsch. Arch. f. klin. Med., 1912, **188**, 1.
3. Lundsgaard, C. J. Biol. Chem., 1918, **33**, 133.
4. Stadie, W. C.: J. Exp. Med., 1919, **30**, 215.
5. Van Slyke, D. D.: J. Biol. Chem., 1918, **28**, 127.
6. Binger, C. A. L.: J. Clin. Invest., 1928, **6**, 203.
7. Stadie, W. C.: J. Exp. Med., 1922, **35**, 337.
8. Harrop, G. A., Jr.: J. Exp. Med., 1919, **30**, 240.
9. Harrison, T. R., and Pilcher, C.: J. Clin. Invest., 1930, **8**, 259.
10. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Vol. I, Interpretations, Baltimore, The Williams & Wilkins Company, 1931, pp. 592 *et seq.*
11. Cannon, W. B., and Haskins, R. G.: Am. J. Physiol., 1911, **29**, 274.
12. Cannon, W. B., and Burket, R.: Am. J. Physiol., 1913, **32**, 347.
13. Palthé, P. M. van W.: Deutsch. Ztschr. f. Nervenh., 1926, **92**, 79.
14. Greene, C. W., and Gilbert, N. C.: Am. J. Physiol., 1922, **60**, 155.
15. Meakins, J. C.: Arch. Int. Med., 1920, **25**, 1.
16. Binger, C. A. L., and Davis, J. S., Jr.: J. Clin. Invest., 1928, **6**, 171.
17. Kline, B. S., and Winternitz, M. C.: J. Exp. Med., 1915, **21**, 311.
18. Gross, L.: Canadian Med. Assn. J., 1919, **9**, 632.
19. Barach, A. L., and Woodwell, M. N.: Arch. Int. Med., 1921, **28**, 415.
20. Binger, C. A. L., Brow, G. R., and Branch, A.: J. Clin. Invest., 1924, **1**, 155.
21. Greene, C. W.: J. Am. Med. Assn., 1925, **85**, 645.
22. Peabody, F. W.: J. Exp. Med., 1913, **18**, 7.
23. Butterfield, G. E., and Peabody, F. W.: J. Exp. Med., 1913, **17**, 587.
24. Peabody, F. W.: J. Exp. Med., 1913, **17**, 1.
25. Strughold, H.: Am. J. Physiol., 1930, **94**, 641.
26. Schneider, E. C., and Truesdell, D.: Am. J. Physiol., 1924, **71**, 90.
27. Smith, J. S.: J. Physiol., 1899, **24**, 19.
28. Benedict, F. G., and Higgins, H. L.: Am. J. Physiol., 1911, **28**, 1.
29. Karsner, H. J.: J. Exp. Med., 1916, **23**, 149.
30. Barach, A. L.: Am. Rev. Tuberc., 1926, **13**, 293.
31. Binger, C. A. L., Faulkner, J. M., and Moore, R. L.: J. Exp. Med., 1927, **45**, 849.
32. Boothby, W. M., and Haines, S. F.: J. Am. Med. Assn., 1928, **90**, 372.
33. Evans, J. H.: Canadian Med. Assn. J., 1930, **22**, 518.
34. Barach, A. L., and Richards, D. W.: To be published.
35. Barach, A. L.: Arch. Int. Med., 1926, **37**, 188.
36. Guedel, A. E.: J. Am. Med. Assn., 1925, **84**, 1490.
37. Wineland, A. J., and Waters, R. M.: Arch. Surg., 1931, **22**, 67.

38. Barach, A. L.: J. Am. Med. Assn., 1929, **93**, 1550.
39. Meakins, J. C.: J. Path. and Bact., 1921, **24**, 79.
40. Barach, A. L., and Woodwell, M. N.: Arch. Int. Med., 1921, **28**, 367.
41. Campbell, J. M. H., Hunt, G. H., and Poultón, E. P.: J. Path. and Bact., 1923, **26**, 234.
42. Rabinowitch, I. M.: Arch. Int. Med., 1925, **36**, 239.
43. Means, J. H., and Newburgh, L. H.: Trans. Assn. Am. Phys., 1915, **30**, 51.
44. Lundsgaard, C.: J. Exp. Med., 1918, **27**, 179.
45. Barach, A. L., and Richards, D. W., Jr.: Arch. Int. Med., 1931, **48**, 325.
46. Barach, A. L.: Ann. Int. Med., 1931, **5**, 428.
47. Hamburger, W. W., Katz, L. N., Cohn, D. J., and Rubinfeld, S. H.: J. Am. Med. Assn., 1932, **94**, 1363.
48. Levy, R. L., and Barach, A. L.: J. Am. Med. Assn., 1930, **94**, 1363.
49. Barach, A. L.: Anesth. and Analg., 1932, p. 71.
50. Barach, A. L., Dickinson, R. W., Milberato, A. I., and Levy, R. L.: Proc. Soc. Exp. Biol. and Med., 1930, **27**, 308.
51. Campbell, J. M. H., and Poulton, E. P.: Quart. J. Med., 1926, **20**, 27.
52. Boothby, W. M., and Haines, S. F.: Am. J. Surg., 1929, **6**, 1.
53. Pemberton, J. DeJ.: N. Y. State J. Med., 1928, **28**, 256.
54. Henderson, Y., and Haggard, H. W.: J. Am. Med. Assn., 1921, **77**, 1065.
55. Coryllos, P. N.: Am. J. Obst. and Gynec., 1931, **21**, 513.
56. Murphy, D. P., Wilson, R. B., and Bowman, J. E.: Am. J. Obst. and Gynec., 1931, **21**, 528.
57. Flagg, P. J.: Am. J. Obst. and Gynec., 1931, **21**, 537.
58. Henderson, Y.: Am. J. Obst. and Gynec., 1931, **21**, 542.
59. Soloman, H. C., Kaufman, M. R., and D'Elseaux, F.: Am. J. Psychiat., 1931, **10**, 761.
60. Seegal, L., and Hinsie, L. E.: Am. J. Med. Sci., 1926, **171**, 727.
61. Judd, E. S., and Passalacqua, L. A.: Clin. North America, (Feb.) 1929, Surg., **9**, 13.
62. Boothby, W. M., and Haines, S. F.: Trans. Am. Phys., 1927, **42**, 287.
63. Rosenbluth, M. D., and Block, M.: J. Am. Med. Assn., 1932, **98**, 396.
64. Henderson, Y., Haggard, H. W., Coryllos, P. N., and Bernbaum, G. L., Jr.: Arch. Int. Med., 1930, **45**, 72.
65. Henderson, Y.: New Eng. J. Med., 1932, **206**, 151.
66. Lord, F. T.: J. Exp. Med., 1919, **30**, 379.
67. Lord, F. T., and Nye, N. N.: J. Exp. Med., 1919, **30**, 389.

LYSOZYME IN SALIVA.

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The interesting researches of Fleming[1] established the presence of lysozyme in human saliva. This lytic agent is so potent that when saliva is diluted 1 to 300 Micrococcus lysodeikticus is com-

pletely dissolved in 1 hour at 45° C. Because of the possible rôle of focal infection in psychotic states[2] Penrose[3] sought "to discover whether any corresponding alteration could be observed in the lysozyme content of the saliva of psychotics as compared with the normal." His tests on 26 psychotic patients and 6 normal controls are summarized as follows: "The figures quoted suggest that there is no significant difference between the normals, mental defectives and cases of dementia præcox with regard to the lysozyme content of saliva, but that in organic psychoses, such as G. P. I. and Parkinsonism (general paralysis and postencephalitic Parkinsonism) the concentration is much diminished."

In view of these findings we undertook an investigation of the lysozyme content of the saliva of 14 postencephalitic patients, 2 general paralytics, 1 acute encephalitic, and 14 laboratory workers of the Psychiatric Institute who graciously volunteered to serve as controls. Through the kind coöperation of Miss Frances J. McClellan, of the Neurologic Institute, we were able to obtain specimens of saliva from the postencephalitic patients.

Procedure. Specimens of saliva were centrifuged for 5 minutes at medium speed immediately after collection and 1 cc. used for the original dilution. Further dilutions were made with physiologic saline. One cubic centimeter of an 18-hour growth of Micrococcus lysodeikticus (averaging 5,000,000,000 organisms) to 9 cc. of diluted saliva yielded the final desired concentration. We are indebted to Prof. Alexander Fleming for very generously supplying us with the original culture. The saliva culture mixture was incubated (within 10 minutes) at 45° C. for 1 hour together with controls of the culture in saline. Seven-eighths or more lysis was considered positive. In order to attain objective accuracy, in our later studies, standard 7/8 tubes were prepared by adding 8.75 cc. of diluent to 1.25 cc. of a 1 to 10 suspension of Micrococcus lysodeikticus. Also when these standard tubes were employed we followed Penrose's suggestion of using equal parts of normal saline and isotonic phosphate buffer solution instead of normal saline so as to obviate any adverse influences of the saliva on the hydrogen-ion concentration. The diluting fluid was, therefore, made up of equal parts of 0.14 molar NaCl and phosphate mixture (2 parts 0.14 molar KH_2PO_4 added to 8 parts of 0.14 molar Na_2HPO_4-$12H_2O$) yielding, according to Sorenson, a final pH of 7.4. Our data in Table 1 have been recorded under two headings—"Preliminary Technique" where physiologic saline was used as a diluent and 7/8 lysis judged by inspection, and "Modified Technique" where a buffered solution of pH 7.4 was employed as a diluent and the lysis was judged by comparison with a standard tube. Readings of 5/8 lysis by the "modified technique" are also included.

Results. From Table 1 it will be seen that of the 14 postencephalitic patients 12 showed lysis at least once in a dilution of 1/300 and 2 in 1/100 with the "preliminary technique."* Of the 14 normal controls 12 showed lysis at least once in a dilution of 1/300 and 1 each in dilutions of 1/100 and 1/200. In other words the results

* Six patients and 4 controls, all of whom showed lysis in a dilution of 1/300, were omitted from Table 1 since only a single specimen was taken.

TABLE 1.—LYTIC ACTION OF SALIVA ON MICROCOCCUS LYSODEIKTICUS.

Cases.	Preliminary technique (7/8 lysis).							Modified technique (7/8 lysis).					5/8 lysis.				
	Dec. 8.†	Dec. 12.	Dec. 15.	Jan. 5.	Jan. 7.	Jan. 12.	Jan. 14.	Mar. 4.	Mar. 16.	June 8.	June 15.	July 9.	Mar. 4.	June 8.	June 15.	July 9.	July 13.
Encephalitis																	
Rr	1/300+	...	1/1200+	1/100+	...	...	...	...	...	...	1/50−	...	...	...	1/50+		
				1/200−	...	...	...	...	...	...	...	...	...	...	1/100−		
Gg	1/300+	...	1/400+	1/100+	...	1/500+	...	...	...	...	1/50−	...	...	...	1/50−		
			1/800+	1/200−	...	1/1000−											
			1/1000−														
Hr	1/300+	...	...	...	...	1/1000+	...	...	...	...	1/100−	...	...	...	1/200+		
															1/300−		
Gl	1/300+	...	1/100+	...	...	...	...	...	...	...	1/50−	...	...	...	1/100+		
			1/400−	...	...	...	...	...	...	...	...	...	...	...	1/200−		
Wr	1/300+	...	1/100+	...	...	1/100+	...	...	...	...	1/100−	1/50−	...	...	1/200+	1/300+	
			1/400±	...	...	1/300−	...	...	...	...	...	...	...	...	1/300−		
			1/800−														
Sn	1/300+	...	1/100+	...	...	1/100+	...	...	...	...	1/25−						
			1/400−	...	...	1/300−											
Ar*	...	...	...	...	...	...	...	1/100−	1/100−	1/50−							
Aa	...	...	...	...	...	1/100+											
						1/300−											
Ge	...	...	...	...	...	1/100+	...	...	...	...	...	1/25−	...	...	...	1/200+	
						1/300−	...	...	...	...	...	...	...	...	...	1/300−	
General paralytics																	
Rh	1/100+																
Sn	1/200+																
Normals																	
Kf	1/300+	1/900+	1/1000+	1/100−	1/300+	1/100+	1/100−	1/100−	1/50−	1/50−	1/25−	1/25−	1/100+	1/25+	1/100+	1/100+	
			1/1500−	...	1/500−	1/300−	...	...	...	...	...	...	1/200−	1/50−	1/200−	1/200−	
Ha	1/100+	...	...	1/100−	...	1/100−	1/100−	1/100−	1/50−	1/25−	1/50−						
Mn	1/300+	1/900+	1/1000+	1/100+	1/300+	1/100+	1/100−	1/100−	1/50−	1/25−	1/25−	1/25−	1/100+	1/50+	1/25+	1/25+	1/100+
			1/1500−	1/200−	1/500−	1/300−	...	...	...	...	...	...	1/200−	...	1/50−	1/50−	1/200−
Bn	1/100+	1/300+	1/100+	1/100−	...	1/100−	1/100−	1/100−	1/50−	1/25−	1/50−	1/25−	...	...	...	1/25+	
			1/400−	...	...	...	...	...	...	...	...	...	...	...	...	1/50−	
Bp	1/300+	...	...	...	...	...	...	...	...	...	1/25−						
Sr	1/300+	...	1/100−	...	...	...	...	...	...	...	1/25−	...	...	...	1/25+		
															1/50−		
Un	1/300+	...	...	...	...	...	...	...	...	...	1/25−						
Wr	...	...	1/1000±	...	...	...	...	...	...	...	1/25−	...	...	...	1/200+		
			1/1200−	...	...	...	...	...	...	...	...	...	...	...	1/300−		
Ca	1/300+	...	1/100−														
Bl	1/300+	...	1/100−														

* Acute encephalitis.

† On this date 6 other cases of encephalitis and 3 normals showed 7/8 lysis at 1/300+.

were the same for postencephalitic patients and normals. With the "modified technique" neither postencephalitic patients nor normals showed 7/8 lysis (in dilutions of 1/25 or upward). If 5/8 lysis is employed as the criterion, then of 6 postencephalitic patients studied 1 showed lysis in 1/300, 2 in 1/200, 1 in 1/100 and 1 in 1/50. Of the 5 normals 1 showed lysis in 1/200, 2 in 1/100 and 2 in 1/50. Again this indicates no lack of lysozyme content in the saliva of postencephalitic patients as compared with normals.

It will be observed that there is considerable variation in the lysozyme content of any individual on repeated tests. Thus Gg, on December 8, 1930, showed lysis in 1/300, on December 15, 1/800, on January 8, 1931, lysis in 1/100 and on January 12 lysis in 1/500 with the "preliminary technique" but failed to show lysis in 1/50 on June 15, 1931 with the "modified technique." The experimental error is obviously too large to permit of any generalizations differentiating postencephalitic patients from normals on this basis.

There is always a possibility in dealing with a bacteriologic test that variations in the culture may be responsible for unaccountable discrepancies. Consequently we investigated the influence of time of incubation of Micrococcus lysodeikticus before use, the age of the culture and the medium upon which it was grown.

TABLE 2.—ACTIVITY OF MICROCOCCUS LYSODEIKTICUS IN BUFFERED POWDERED EGG ALBUMEN SOLUTION.

Date, 1931.	Albumen.	"Old culture."		"New culture."	
		7/8 lysis.	5/8 lysis.	7/8 lysis.	5/8 lysis.
Mar. 20	A	1/10,000+			
April 16	A	1/10,000+			
	B	1/10,000+	...	1/10,000+	
20	B	1/10,000+	1/19,000+	1/10,000+	1/19,000+
		1/13,000−	1/21,000−	1/13,000−	1/21,000−
June 8	B	1/10,000+	1/15,000+		
		1/12,000−	1/20,000−		
11	B	...	...	1/10,000+	1/15,000+
				1/12,000−	1/20,000−
15	B	...	...	1/8,000+	1/15,000+
				1/10,000−	1/20,000−
15	C	...	...	1/10,000+	1/25,000+
				1/12,000−	
26	C	...	...	1/8,000+	1/15,000+
				1/10,000−	

The first culture of Micrococcus lysodeikticus grown on casein digest agar was incubated for 18 hours on casein digest agar, and from this a saline suspension was made which had a microscopic count of 6,500,000,000 organisms per cc. The second culture was incubated for 16 hours and had a count of 5,000,000,000 per cc.

Thereafter we employed 48-hour growths made up to a nephelometric standard to yield a final count of 5,000,000,000 organisms per cc. In this way the number of Micrococcus lysodeikticus used at each test was constant and of the same age. The transfers were made serially from the culture sent us originally by Professor Fleming. Thinking that perhaps continued transfers had weakened or strengthened the culture, we started new transfers in April from a duplicate which had been ice-boxed since November. This change had no appreciable influence on our results. The cultures are labeled "old" and "new," respectively, in Table 2.

As a final check on the activity of the culture, powdered egg albumen which is known to have lytic properties was made up with buffered solution, filtered, and toluene added as a preservative. Repeated tests with samples A, B and C yielded uniform results which are recorded in Table 2.

In an attempt to make the "new" culture more susceptible to lysis it was grown on beef extract agar. In Table 3 are recorded the results of tests with buffered powdered egg albumen solution.

TABLE 3.—INFLUENCE OF MEDIUM ON LYSIS OF MICROCOCCUS LYSODEIKTICUS BY EGG ALBUMEN.

Agar medium.	Number of transfers.	7/8 lysis.	5/8 lysis.
Casein digest	15	1/8,000+	1/15,000+
		1/10,000−	1/20,000−
Beef extract	5	1/10,000+	1/30,000+
		1/12,000−	1/40,000−
Beef extract	12	1/15,000+	1/30,000+
		1/17,000−	1/40,000−
Beef extract	14	1/17,000+	1/30,000+
		1/20,000−	1/40,000−

From Table 3 it will be seen that susceptibility to lysis was somewhat increased by growing the culture on beef extract agar instead of casein digest agar. No striking change in colony formation was observed. One might speculate on the possibility of increasing the susceptibility of Micrococcus lysodeikticus still further by adaptation to more appropriate media. However, from the studies just described it may be inferred that Micrococcus lysodeikticus is a stable culture which does not vary markedly under different conditions of growth, and that it is therefore admirably suited for the purpose which Fleming suggested, namely, a measure of the lytic principle present in human secretions.

Summary. 1. Human saliva contains lysozyme, the activity of which may be measured by the dissolution of Micrococcus lysodeikticus as described by Fleming.[1]

2. No differences could be discerned between the lysozyme content of postencephalitic patients and normals when accurate standards were employed. This is contrary to the findings of Penrose.[3]

3. Neither the age of the culture nor the incubation period within the limits indicated have any significant influence on the test.

4. The composition of the medium, however, does exert an appreciable influence on the susceptibility of Micrococcus lysodeikticus to lysis.

BIBLIOGRAPHY.

1. Fleming, A.: Lysozyme: A Bacteriolytic Ferment Found Normally in Tissues and Secretions, Lancet, 1929, 1, 217.
2. Kopeloff, N., and Kirby, G. H.: Focal Infection and Mental Disease, Am. J. Psychiat., 1923, 3, 149.
3. Penrose, L. S.: The Lysozyme Content of Saliva in Psychotics, Lancet, 1930, 2, 689.

A STUDY OF "IRON VOLUME INDEX" OF THE BLOOD AND ITS SIGNIFICANCE IN THE TREATMENT OF ANEMIA.

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In his "De Ferrearum Particularum Sede in Sanguine," published in 1746, Menghini[1] first called attention to the presence of iron in the blood. Since this time many papers have been written on the subject, dealing, however, almost entirely with the methods for determining the iron, the quantities in which it is present in the blood and the correlation between the iron and the hemoglobin. An excellent review of this literature may be found in an article of recent date by Murphy, Lynch and Howard.[2] These investigators went a step further and established an iron index, the purpose of which was to aid in differentiating and treating the various types of anemia. This index was calculated by dividing the milligrams of iron per 100 cc. of whole blood by the red blood count expressed in millions per cubic millimeter. The average iron index was 8.46, and Murphy and his coworkers considered it analogous to the well known color index, only more reliable.

Recently, however, Haden,[3] Wintrobe,[4] Osgood,[5] and others have emphasized the importance of determining the size of the red blood cell and of correlating this information with other data such as the number of the red blood cells and their hemoglobin content. These determinations are known as the volume index and the saturation index. The volume index expresses the relationship between the cell volume and the number of cells, while the saturation index

NORMALS.

Case.	Sex.	Age.	Diagnosis.	Hb., gm. per 100 cc.	Hb., %.	R.B.C., millions per c.mm.	Cell vol., per 100 cc.	Iron, mg. per 100 cc.	Volume index.	Saturation index.	Iron volume index.	Average vol. of erythrocyte, cubic microns.	Average Hb. per erythrocyte, gm. $\times 10^{-11}$ Hbe	Average iron per erythrocyte, mg. $\times 10^{-11}$ Ie	Hbe / Ie
1 . .	M	35	Chronic cardiac valvular disease	13.7	88	4.5	41	40.0	0.99	0.98	0.97	91.1	1.24	3.64	340
2 . .	M	47	Tabes	14.8	96	5.1	44	44.1	0.93	1.00	1.00	86.2	1.27	3.80	334
3 . .	M	37	Gastric neurosis	15.6	100	5.3	48	48.5	0.98	0.95	1.00	90.5	1.41	4.38	321
4 . .	M	17	Chronic tonsillitis	13.5	87	4.6	42	43.5	0.99	0.95	1.00	91.3	1.23	3.97	309
5 . .	M	21	Gastric neurosis	16.6	107	5.8	49	50.0	0.91	1.00	1.00	84.4	1.40	4.22	326
6 . .	M	60	Acute bronchitis	14.0	90	4.5	40	42.0	0.96	0.96	1.00	88.8	1.24	3.61	343
7 . .	M	53	Angina pectoris	13.5	87	4.4	40	41.0	0.98	1.00	1.00	90.9	1.22	3.72	327
8 . .	M	45	Gastric neurosis	14.0	90	4.6	41	42.1	0.97	0.98	1.00	89.1	1.24	3.75	330
9 . .	M	31	Blood donor	15.6	100	5.0	45	43.0	0.97	1.00	0.95	90.0	1.40	3.87	361
10 . .	M	32	Pneumonia	13.2	85	4.6	40	41.0	0.94	0.97	1.00	87.0	1.14	3.56	320
11 . .	M	46	Cardiac neurosis	14.0	90	4.6	42	41.7	0.99	0.98	0.99	91.3	1.27	3.80	334
12 . .	M	58	Gastric neurosis	14.8	95	4.9	45	46.3	0.98	1.00	0.95	91.7	1.35	4.24	318
13 . .	M	33	Sacroiliac disease	12.6	81	4.2	38	40.1	0.98	0.98	1.00	90.4	1.13	3.62	359
14 .	M	22	Cut tendons of hand	14.0	90	4.7	42	43.1	0.97	0.98	1.00	85.1	1.19	3.66	325
15 . .	M	25	Cardiac neurosis	15.6	100	5.0	46	48.7	1.00	1.00	1.00	92.0	1.43	4.48	319
16 . .	M	30	Gastric neurosis	14.0	90	4.7	42	42.0	0.99	0.98	1.00	89.3	1.25	3.75	333
17 . .	M	40	Laceration of hand	14.3	92	4.8	44	46.0	0.99	0.92	1.00	91.6	1.30	4.21	308
18 . .	M	31	Kidney stone	14.0	90	4.7	42	42.2	0.97	0.98	1.00	89.3	1.25	3.76	332
19 . .	M	50	Contusion of leg	13.8	89	4.5	41	42.5	0.99	0.99	0.96	91.0	1.25	3.86	323
20 . .	M	20	Grippe	13.7	88	4.6	40	36.8	0.99	1.00	0.92	91.1	1.24	3.35	370
21 . .	M	54	Diabetes	14.0	90	4.7	42	40.4	0.97	0.98	0.96	89.3	1.25	3.60	347
22 . .	M	40	Ulcerative colitis	14.8	95	5.4	48	40.4	0.97	0.91	0.84	88.8	1.31	3.58	365
23 . .	F	68	Chronic myocarditis	12.4	80	4.2	36	38.8	0.93	1.00	1.00	85.7	1.06	3.42	309
24 . .	F	40	Chronic appendicitis	12.7	82	4.4	40	43.5	0.98	0.94	1.00	90.9	1.15	3.95	291
25 . .	F	32	Gastric neurosis	12.4	80	4.0	36	38.1	0.97	1.00	1.00	90.0	1.16	3.42	339
26 . .	F	31	Chronic appendicitis, operation	14.8	95	4.9	45	42.5	0.99	0.97	0.94	91.8	1.35	3.90	343
27 . .	F	47	Acute appendicitis, operation	13.2	85	4.5	40	37.4	0.96	0.97	0.93	88.8	1.17	3.31	353
28 . .	F	30	Chronic salpingitis, Wass. 4+	13.2	85	4.6	40	36.4	0.94	0.97	0.91	86.9	1.14	3.16	360
29 . .	F	55	Chronic alcoholism	13.5	87	4.7	43	43.2	0.99	0.94	1.00	91.4	1.23	3.94	310
30 . .	F	40	Chronic salpingitis	12.4	80	4.3	39	42.5	0.98	0.94	1.00	90.7	1.12	3.85	290
31 . .	F	38	Chronic arthritis	14.0	90	4.9	42	44.4	0.93	0.98	1.00	85.7	1.20	3.80	316
32 . .	F	65	Chronic myocarditis	15.6	100	5.0	45	42.7	0.99	1.00	0.95	90.0	1.40	3.84	364
33 . .	F	38	Chronic arthritis	14.1	91	4.7	43	37.4	1.00	0.97	0.87	91.4	1.28	3.41	375
34 . .	F	39	Sciatica	14.3	92	4.6	44	45.0	0.95	0.96	1.00	95.6	1.36	4.30	316
35 . .	F	64	Chronic arthritis	15.6	100	5.0	45	45.0	0.98	1.00	1.00	90.0	1.40	4.05	345
36 . .	F	23	Influenza	12.9	83	4.4	40	42.5	0.99	0.95	1.00	90.9	1.17	3.86	303
37 . .	F	23	Influenza	13.2	85	4.4	40	43.0	0.99	0.94	1.00	91.1	1.19	3.91	304

			Sciatica	14.3	92	4.6	44	45.0	0.95	0.96	1.00	95.6	1.36	4.30	316
35	F	64	Chronic arthritis	15.6	100	5.0	45	45.0	0.98	1.00	1.00	90.0	1.40	4.05	345
36	F	23	Influenza	12.9	83	4.4	40	42.5	0.99	0.95	1.00	90.9	1.17	3.86	303
37	F	25	Catarrhal jaundice	13.1	84	4.5	41	43.0	0.99	0.94	1.00	91.1	1.19	3.91	304
38	F	49	Exophthalmic goiter	12.6	81	4.4	41	40.5	1.00	0.90	1.00	93.1	1.17	3.77	300
39	F	51	Cellulitis of arm	14.1	91	4.7	43	43.5	0.99	0.97	1.00	91.4	1.27	3.87	302
40	F	35	Glandular fever	13.4	86	4.6	40	40.7	0.99	0.98	1.00	86.9	1.16	3.53	328
41	F	50	Chronic arthritis	15.6	100	5.0	44	47.6	0.95	1.00	1.00	88.8	1.38	4.21	325
42	F	60	Arteriosclerosis	14.0	90	4.5	41	43.5	0.99	1.00	1.00	91.3	1.27	3.97	319
43	F	30	Chronic bronchitis	14.0	90	4.8	41	42.5	0.92	1.00	1.00	85.4	1.19	3.52	338
44	F	42	Chronic bronchitis	12.4	80	4.2	37	40.7	0.95	0.99	1.00	88.0	1.09	3.58	304
45	F	40	Chronic arthritis	14.0	90	4.8	42	43.4	0.92	0.98	1.00	87.4	1.22	3.79	321

ANEMIAS (IRON VOLUME INDEX 1).

Case.	Sex.	Age.	Diagnosis.	Hb., gm. per 100 cc.	Hb., %.	R.B.C., millions per c.mm.	Cell vol., per 100 cc.	Iron, mg. per 100 cc.	Volume index.	Saturation index.	Iron volume index.	Average vol. of erythrocyte, cubic microns.	Average Hb. per erythrocyte, gm. $\times 10^{-11}$ Hbe	Average iron per erythrocyte, mg. $\times 10^{-11}$ Ie	$\frac{\text{Hbe}}{\text{Ie}}$
1	M	56	Cirrhosis of liver	11.7	75	4.2	35	37.0	0.90	0.98	1.0	83.3	0.97	3.08	314
2	F	48	Pernicious anemia	1.7	75	3.4	35	37.0	1.11	0.98	1.0	102.9	1.20	3.80	315
3	M	58	Pernicious anemia	14.0	90	4.2	42	44.5	1.08	0.98	1.0	100.0	1.40	4.45	315
4	M	28	Pulmonary tuberculosis	11.7	75	4.2	39	40.0	1.00	0.88	1.0	92.8	1.08	3.71	291
5	F	43	Carcinoma of stomach	12.6	81	4.5	38	40.3	0.91	0.98	1.0	84.4	1.06	3.40	311
6	F	39	Carcinoma of stomach	4.9	32	2.0	16	16.3	0.86	0.92	1.0	80.0	0.39	1.30	300
7	F	42	Carcinoma of cervix	5.9	38	.26	20	21.1	0.83	0.87	1.0	76.9	0.45	1.62	277
8	M	21	Pneumonia	10.9	70	3.6	35	36.4	0.99	0.92	1.0	97.2	1.07	3.53	303
9	F	50	Chronic cardiovascular disease	10.1	65	3.3	30	32.4	0.98	0.99	1.0	90.9	0.91	2.94	309
10	M	45	Gastr. ulcer, possibly carcinoma	10.7	69	3.7	34	37.0	0.99	0.93	1.0	91.8	0.98	3.39	289
11	M	30	Pneumonia	7.8	50	2.8	24	26.0	0.93	0.95	1.0	85.7	0.67	2.22	301
12	F	55	Hodgkin's disease	6.3	41	2.4	24	26.0	0.95	0.78	1.0	100.0	0.63	2.60	242
13	M	15	Lymphatic leukemia	5.4	35	2.1	19	21.3	0.99	0.84	1.0	90.4	0.48	1.92	250
14	F	54	Carcinoma of liver	6.24	40	2.6	19	79.5	0.80	0.96	1.0	70.8	0.44	1.41	312
15	F	26	Acute bronchitis	11.7	75	4.1	37	38.3	0.97	0.98	1.0	90.2	1.05	3.45	304
16	F	67	Carcinoma of liver	9.67	62	3.6	33	35.1	0.98	0.86	1.0	91.3	0.89	3.20	278
17	F	61	Carcinoma of pancreas	9.51	61	3.4	31	32.5	0.99	0.90	1.0	91.1	0.86	2.96	294
18	M	53	Carcinoma of rectum	7.02	45	2.4	22	23.2	0.98	0.94	1.0	91.6	0.64	2.45	261
19	F	62	Chronic cholecystitis	10.1	65	3.3	30	30.3	0.97	0.99	1.0	90.9	0.91	2.75	330
20	F	23	Septic endometritis	7.8	50	3.0	23	23.3	0.97	0.95	1.0	76.6	0.59	1.78	331
21	F	43	Tertiary lues	10.9	70	3.6	32	34.0	0.96	1.00	1.0	88.8	0.96	3.01	315
22	M	23	Chancroid	11.7	75	3.9	35	36.7	0.97	0.98	1.0	89.7	1.04	3.27	315
23	F	39	Tabes	10.9	70	3.7	32	33.5	0.94	0.99	1.0	86.4	0.94	2.89	332
24	M	46	Influenza	11.0	71	3.7	33	35.7	0.96	0.98	1.0	89.1	0.98	3.12	314

ANEMIAS (IRON VOLUME INDEX 1)—*Continued.*

Case.	Sex.	Age.	Diagnosis.	Hb., gm. per 100 cc.	Hb., %.	R.B.C., millions per c.mm.	Cell vol., per 100 cc.	Iron mg. per 100 cc.	Volume index.	Saturation index.	Iron volume index.	Average vol. of erythrocyte, cubic microns.	Average Hb. per erythrocyte. gm. $\times 10^{-11}$ Hbe	Average iron per erythrocyte, mg. $\times 10^{-11}$ Ie	Hbe / Ie
25 . .	F	74	Chronic nephritis	10.9	70	3.8	35	37.5	0.97	0.94	1.0	92.1	1.00	3.45	287
26 . .	F	60	Lymphatic leukemia	10.9	70	3.6	32	34.0	0.99	1.00	1.0	88.8	0.96	3.01	318
27 . .	F	61	Chronic myocarditis	11.8	76	4.0	36	38.3	0.98	0.97	1.0	90.0	1.06	3.44	306
28 . .	F	59	Arteriosclerosis	10.1	65	3.4	31	33.0	0.99	0.96	1.0	91.1	0.92	3.00	306
29 . .	F	51	Chronic myocarditis	9.2	59	3.7	27	30.4	0.92	1.00	1.0	84.3	0.77	1.76	438
30 . .	F	42	Acute appendicitis	12.1	78	4.0	36	36.7	0.97	0.99	1.0	90.0	1.08	3.30	321
31 . .	F	63	Chronic cholecystitis	11.8	76	4.0	36	38.1	0.97	0.97	1.0	90.0	1.06	3.42	349
32 . .	M	50	Chronic myocarditis	10.1	65	3.6	30	32.4	0.90	0.99	1.0	83.3	0.84	2.69	312
33 . .	F	25	Pulmonary tuberculosis	10.9	70	4.0	36	37.5	0.97	0.89	1.0	90.0	0.98	3.37	290
34 . .	F	58	Arteriosclerosis	10.9	70	3.9	35	37.1	0.94	0.92	1.0	92.0	0.98	3.41	281
35 . .	F	49	Chronic arthritis	11.3	73	3.8	34	36.3	0.97	0.98	1.0	89.4	1.01	2.90	344
36 . .	F	70	Pernicious anemia	11.5	74	3.2	36	38.4	1.20	0.94	1.0	112.3	1.29	4.31	276
37 . .	M	30	Exophthalmic goiter	9.9	64	3.3	30	32.2	0.98	0.98	1.0	90.9	0.89	2.92	304
38 . .	M	60	Carcinoma of rectum	9.6	62	3.2	29	29.0	0.99	0.98	1.0	90.6	0.86	2.62	328
39 . .	F	35	Chronic sinusitis	11.7	75	3.9	34	34.4	0.94	1.00	1.0	87.2	1.02	2.99	341
40 . .	M	21	Diabetes	12.1	78	4.0	36	38.0	0.97	0.99	1.0	90.0	1.08	3.42	315
41 . .	M	50	Duodenal ulcer	12.4	80	4.1	42	43.5	0.91	0.87	1.0	102.4	1.27	4.45	285
42 . .	F	20	Carcinoma of stomach	11.7	75	4.0	36	38.2	0.97	0.95	1.0	90.0	1.05	3.43	306
43 . .	M	62	Carcinoma of rectum	11.5	74	3.8	34	35.7	0.97	1.00	1.0	89.4	1.02	3.17	320
44 . .	F	50	Carcinoma of gall bladder	10.9	70	3.7	34	34.4	0.99	0.91	1.0	91.9	1.00	3.16	316

ANEMIAS (IRON VOLUME INDEX LESS THAN 1).

Case.	Sex.	Age.	Diagnosis.	Hb., gm. per 100 cc.	Hb., %.	R.B.C., millions per c.mm.	Cell vol., per 100 cc.	Iron, mg. per 100 cc.	Volume index.	Saturation index.	Iron volume index.	Average vol. of erythrocyte, cubic microns.	Average Hb. per erythrocyte, gm. $\times 10^{-11}$ Hbe	Average iron per erythrocyte, mg. $\times 10^{-11}$ Ie	Hbe / Ie
1 . .	M	63	Gastric ulcer	12.4	80	4.1	37	34.0	0.98	0.89	0.91	90.2	1.11	3.06	362
2 . .	M	60	Bronchiectasis	8.1	52	2.9	24	23.4	0.89	0.99	0.97	82.7	0.66	1.93	342
3 . .	F	14	Perinephritic abscess	7.0	45	2.4	21.5	19.6	0.97	0.96	0.91	89.5	0.61	1.75	348
4 . .	F	22	Miscarriage, hemorrhage	6.8	44	3.0	27	25.6	0.97	0.75	0.94	90.0	0.61	2.30	265
5 . .	F	20	Incompl. abortion, hemorrhage	10.1	65	3.9	32	29.0	0.89	0.93	0.90	82.0	0.82	3.31	243
6 . .	F	22	Incompl. abortion, hemorrhage	7.0	45	2.7	22	18.0	0.88	0.94	0.81	81.4	0.56	1.46	282
7 . .	F	45	Fistula of colon	11.2	72	3.8	34	32.0	0.97	0.97	0.94	89.3	0.90	2.85	317
8 . .	F	27	Chr. endometritis, menorrhagia	7.8	50	3.0	25	22.0	0.90	0.92	0.88	83.3	0.64	1.83	350
9 . .	F	55	Essential hypertension	11.7	75	4.2	35	33.2	0.95	0.98	0.94	83.3	0.97	2.68	362
10 . .	F	20	Abortion, hemorrhage	11.8	76	4.0	36	32.0	0.97	0.96	0.89	90.0	1.06	2.88	357
11 . .	F	31	Pulmonary tuberculosis	9.3	60	3.1	28	25.0	0.98	0.96	0.89	90.3	0.83	2.25	373
12 . .	F	35	Carcin. of kidney, hematuria, nephrectomy	9.3	60	3.3	28	25.0	0.92	0.98	0.93	84.8	0.78	2.12	367

expresses the amount of hemoglobin per unit volume of cell in relation to normal. The color index gives us the amount of hemoglobin per cell in relation to normal but does not take into consideration the cell volume. The iron index of Murphy has a similar defect, expressing iron in relation to the number of red blood cells without considering their volume.

The present studies are intended to establish a new corpuscular iron index which considers whole blood iron as related to cell volume. It is calculated by dividing the iron as expressed by percentage of normal by the cell volume as expressed by percentage of normal. In each case the average volume of the erythrocyte and average hemoglobin and iron per erythrocyte were also calculated. There seems to be some relationship between the hemoglobin and the iron content of the blood, and this was expressed by dividing the hemoglobin per erythrocyte by the iron per erythrocyte. The volume index and the saturation index were tabulated in each instance to aid in correlating the iron content of the cells with their size and hemoglobin content. These studies were carried out on 100 hospital patients. About half were normals. By normals we mean hospital patients showing no anemia and therefore, presumably, no derangement in their iron metabolism. The other half are patients suffering from anemias of the usual types.

Technique. Twenty cubic centimeters of blood are withdrawn from the arm vein and 10 cc. are run into a 15-cc. graduated centrifuge tube containing 2 cc. of a 1.6 per cent sodium oxalate solution. This is mixed by inverting, and centrifuged at 2500 r. p. m. for 1 hour. The total cell volume per cent is then read off and calculated for 100 cc.

The other 10 cc. are shaken up in a test tube previously prepared by evaporating 2 cc. of 1.6 per cent iron-free sodium oxalate solution to dryness. The sodium oxalate used was obtained from the Bureau of Standards and shown by controls to contain no iron. This blood is used for hemoglobin, red blood cell and iron determinations. The hemoglobin was done by both the Sahli and Newcomer methods in each case, and 15.6 gm. of hemoglobin were taken as 100 per cent. Red blood cell counts were done with two standardized pipettes, a drop from each being counted for every determination, and the two averaged. Results were not accepted if the error was more than 2 per cent.

Although several methods have been proposed for the determination of iron in the blood, no one method was found that would meet all the conditions necessary for accuracy and convenience. The simplest method for digestion of the blood uses the sulphuric acid-potassium perchlorate mixture proposed by Wong.[6] However, this author uses an aqueous solution of ferric sulphocyanate for the colorimetric quantitative procedure. The color is due to nonionizable ferric sulphocyanate, the aqueous solutions of which hydrolyze very rapidly, thus making this method inaccurate.

Further improvements in iron determinations consisted in the extraction of this color with amyl alcohol, ether, or a combination of both, and the procedure of Stokes and Cain[7] employing these mediums was found to be the most accurate and satisfactory. By this method the colors obtained are pure and do not fade. The possibility of the reduction of the ferric ion is eliminated by the use of persulphate. The oxidation of the sulphocyanic acid to isopersulphocyanic acid, which is yellow and interferes seriously

with the matching of the colors, is prevented by the use of the double salt of mercuric sulphocyanate sulphocyanic acid. The only objectionable feature of this method is the amyl alcohol, which is very irritating to the mucous membranes of the nose and throat of the investigator. The amyl alcohol may be replaced by the extraction mixture proposed by Bernhard and Drekter,[8] which was found to be just as efficient, nonirritating, and the colors are more easily matched.

Reagents. *Standard Iron Solution. Standard A:* Dissolve 0.702 gm. ferrous ammonium sulphate in about 50 cc. of water. Add 20 cc. of 10 per cent iron-free sulphuric acid. Warm and then add $\frac{N}{10}$ potassium permanganate until a faint pink color persists. Dilute to 1 liter; 1 cc. will contain 0.1 mg. of iron. *Standard B:* Standard A diluted with an equal volume of water; 1 cc. will contain 0.05 mg. of iron.

Sulphocyanic Acid. One hundred grams of ammonium thiocyanate are dissolved in 100 cc. of 65 per cent by weight sulphuric acid. Measure volume, transfer to separatory funnel and shake out immediately with three-fourths volume of amyl alcohol. Discard the aqueous solution and again shake out twice with an equal volume of water. Combine the water extracts, which together contain about 7 per cent of sulphocyanic acid. Saturate with mercuric sulphocyanate so that some remains on the bottom. Allow to stand over night in a dark bottle.

Persulphate Solution. A saturate solution of C. P. iron-free sodium persulphate in distilled water.

Extraction Mixtures. (1) Five parts of amyl alcohol and 2 parts of ether; (2) equal parts of ethylene glycol monobutyl ether and ethyl ether.

Formula for Figuring the Iron.

$$S \times \frac{Rs}{Rx} \times 500 = \text{mg. of iron.}$$

S = strength of standard.
Rs = reading of standard.
Rx = reading of unknown.

Calculations:

$$\text{Volume index} = \frac{\frac{Cv}{46}}{\frac{RV}{5.0}} \quad \begin{matrix} \text{Total cell volume, per cent} \\ \text{Normal cell volume, per cent} \\ \text{R. B. C. in millions} \\ \text{Normal R. B. C. in millions} \end{matrix} \quad \frac{\frac{46}{46}}{\frac{5}{5}} = 1 \qquad \text{Normal values.}$$

$$\text{Saturation index} = \frac{\frac{Hb\%}{100}}{\frac{Cv}{46}} \quad \frac{\frac{100}{100}}{\frac{46}{46}} = 1$$

$$\text{Corpuscular iron index} = \frac{\frac{I}{45}}{\frac{Cv}{46}} \quad \begin{matrix} \text{Iron in mg. per 100 cc.} \\ \text{Average iron in mg. per 100 cc.} \end{matrix} \quad \frac{\frac{45}{45}}{\frac{46}{46}} = 1$$

$$\text{Average volume of erythrocyte (Ev)} = \frac{Cv \times 10^{12}}{Rm \times 10^{11}} \text{ cubic micron } \frac{46^{12}}{5^{11}} = 92$$

$$\text{Average Hb per erythrocyte (Hbe)}^* = Hb\text{ (gm.)} \times Ev \times 10^{-14} = (15.6 \times 92) = [1.43$$

$$\text{Average iron per erythrocyte (Ie)}^* = I \times Ev \times 10^{-14} = (45 \times 92)^{-3} = 4.4$$

* In the tables these determinations, namely, average Hb and average iron, are expressed as $\times 10^{-11}$ by pointing off three more places.

The ether does not have to be of special purity, as the presence of mercuric sulphocyanate prevents the oxidation of the sulphocyanic acid by the peroxids in the ether.

IRON DETERMINATIONS. One cubic centimeter of blood is diluted with 4 cc. of water and 1 cc. of the mixture is digested according to the method of Wong. After being allowed to cool it is diluted to approximately 10 cc. and a drop of persulphate is added, followed by exactly 25 cc. of the extraction medium and 5 cc. of the sulphocyanic acid reagent. The tube is then tightly fitted with a rubber stopper, the mixture is well shaken and after a few minutes' standing separates into two distinct layers. If this separation does not take place rapidly it can generally be accelerated by the addition of a few cubic centimeters of water. One cubic centimeter each of Standards A and B are then digested and treated in the same manner. The A Standard is suitable for figures within the normal range (35 to 50) and the B Standard is used where the iron values are lower than the normal. Since the A Standard contains 0.1 mg. of iron and the B Standard 0.05 mg. of iron, and 0.2 cc. of blood are used, the formula for figuring the iron is as found on p. 642.

Discussion. Analysis of the data shows that the majority of the normal cases have an iron volume index of 1. In a small number it is between 0.9 and 1, so that 0.9 can be taken as the lower limit of normal. When the iron volume index is 1 it means that the red blood cells are saturated with iron and it is to be expected that there will be no response to iron therapy. Strange as it may seem, the majority of the anemias also have an iron volume index of 1, and this would mean that in these cases of anemia, iron is also of no value. This is easily understood in the cases of pernicious anemia, leukemia and Hodgkin's disease. There are, however, a large number of patients with secondary anemia in this group and these require more detailed explanation. The latter are noticeably mostly patients with carcinoma or those suffering from acute or chronic infections with fever. In their report on the treatment of secondary anemia with iron, Smithburn, Masters and Zerfas[9] state that patients suffering from the diseases just mentioned do not respond readily to iron therapy. They give as a reason that fever, infection or intoxication may be responsible for temporary or complete inhibition of the hematopoietic response to iron. In our series such cases show an iron volume index of 1. This seems to indicate that the lack of response to iron treatment is due to the fact that the cells are already saturated with iron rather than that toxic influences are depressing the bone marrow. Those cases of anemia in which the iron volume index is under 0.9 are notably patients who have suffered from direct loss of blood or from some nutritional disorder. It is interesting to note here that two of the normals also had an iron volume index of less than 0.9 despite a normal hemoglobin and red blood cell count. According to our theory the red blood cells are not completely saturated with iron when the iron volume index is below 0.9, and iron should be of therapeutic value in these cases. This experimental observation is

borne out clinically, as we know that patients with secondary anemia following hemorrhage respond most readily to iron treatment.

The iron volume index determination seems to be of value, therefore, in determining which case of anemia will respond to iron. If the red cells are already saturated with iron, as shown by a normal index, further iron therapy is useless.

The determinations of hemoglobin and iron per red cell, while largely of academic interest, indicate quite plainly the well known lack of parallelism between the quantities of hemoglobin and iron in the blood. Iron has a definite place in the hemoglobin molecule, and the relationship of molecular hemoglobin and molecular iron is about 300.[10] Our ratio $\frac{\text{Hb.}}{\text{I}}$ is subject to considerable error, but in some cases there are wide variations above and below that figure which cannot be considered within the limit of error. When the ratio is much lower than 300 it means that there is more iron than can combine with the hemoglobin. This excess iron may be in a prehemoglobin state or in the form of some decomposition product of hemoglobin. When the ratio is much higher than 300 there appears to be more hemoglobin than iron. This might indicate that the hemoglobin is in molecular combination with other substances besides iron, or that other substances besides hemoglobin give its color reaction.

Further investigations on these subjects are planned.

Conclusions. 1. A new corpuscular iron index has been devised in an attempt to correlate the iron in whole blood with cell volume.

2. The normal figure for this index is between 0.9 and 1.0 and when this index is 1.0 the red cells are regarded as saturated with iron.

3. An iron volume index of 1.0 is obtained in most normal people and in cases of pernicious anemia, leukemia and in secondary anemias associated with carcinoma and acute and chronic infections with fever. Iron therapy seems to be of no value in these cases, due to the fact that the red cells are already saturated with iron.

4. An iron volume index of less than normal is most commonly found in cases of secondary anemia caused by malnutrition or loss of blood. Iron is of decided therapeutic value in the treatment of these patients.

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BIBLIOGRAPHY.

1. Menghini: Quoted in Arch. de méd. d. enfants, 1930, **33**, 668.

2. Murphy, W. P., Lynch, R., and Howard, I. M.: The Value of Determinations of the Iron Content of Whole Blood, Arch. Int. Med., 1931, **47**, 883.

3. Haden, R. L.: Methods and Clinical Value of the Determination of the Size of the Red Blood Cell, AM. J. MED. SCI., 1931, **181**, 597.

4. Wintrobe, M. M.: Volume and Hemoglobin Content of Red Blood Corpuscle. Simple Method of Calculation, Normal Findings and Value of Such Calculations in Anemias, Am. J. Med. Sci., 1929, **177**, 513.
5. Osgood, E. E.: Hemoglobin, Color Index, Saturation Index and Volume Index Standards. Redeterminations Based on Findings in 137 Healthy Young Men, Arch. Int. Med., 1926, **37**, 685.
6. Wong, S. Y.: J. Biol. Chem., 1923, **55**, 422.
7. Stokes, H. N., and Cain, J. R.: Yoe's Photometric Chemical Analysis, John Wiley & Son, 1928, **1**, 218.
8. Bernhard, A., and Drekter, I. J.: To be published.
9. Smithburn, K. C., Masters, J. M., and Zerfas, L. G.: The Treatment of Secondary Anemia, J. Lab. and Clin. Med., 1931, **16**, 858.
10. McLeod, J. J. R.: Physiology and Biochemistry in Modern Medicine, St. Louis, C. V. Mosby Company, 1920, p. 92.

THE CLINICAL VALUE OF THE UNCORRECTED COLOR INDEX AND OF CELL SIZE IN PERNICIOUS ANEMIA.

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Confusion concerning the hemoglobin content of the red blood cells,[1] and the inaccuracy of many hemoglobin estimations as compared with van Slyke's method,[2] cast doubt on the value of the uncorrected color index in the diagnosis of pernicious anemia. Many observers, as Herz, Capps, Wroth, Larabee and Rossdale, stress the preferability of the "volume index," as based on more accurate laboratory methods, while Haden,[1] in 1925, pointed out the value of the "saturation index." Osgood[3] used the "hemoglobin coefficient" and "volume coefficient" as simplifying Haden's calculations, while Wintrobe[4] offered the "absolute cell determinations" as substitutes.

The commonness of color index estimation, without any correction, its ease and facility, and the interpretation given results, make it important diagnostically to establish the true value of the routine color index.

The color index $\left(\frac{\%\text{ of hemoglobin}}{\%\text{ of red blood cells}}\right)$ is based on the assumption that a normal person has 100 per cent hemoglobin and a red blood cell count of 5,000,000 cells as equivalent to 100 per cent. These figures do not take into consideration such variable factors

as sex, age, size, altitude, time of day, the different "normal" values of hemoglobin, and the like; thus representing an "uncorrected" rather than a "corrected" color index.

The figures for average normal red blood cell counts (5,000,000 per c.mm. for men and 4,500,000 for women) were adopted a long time ago, and continued without proper confirmation. Vierordt (1852) and Welcker (1854), each of whom examined the blood of only 2 persons are responsible for these figures. Recently Osgood,[3] Rud, Wintrobe and Miller, Horneffer, Komicki and Haden have published more accurate data on normal averages in various localities, finding a wide range of variations, with averages ranging from 4,870,000 to 5,600,000 red cells per cu. mm. Because of the unavoidable error in the method of counting the red blood cells, which may amount to 250,000±, 5,000,000 is arbitrarily assumed as normal in calculating the results obtained.

The literature on normal hemoglobin standards is of but slight value because so many different methods of hemoglobin estimations have been used. Most observers have employed hemoglobinometers graduated to read in per cent with no agreement as to what shall be the equivalent to 100 per cent. In compiling the data to be discussed later, the Sahli hemoglobinometer (Leitz), in which 14 gm. of hemoglobin are equivalent to 100 per cent, was used, calibrated and checked with the van Slyke[2] gas method.

A third factor to be considered as related to the color index is the measurement of red blood cell diameters. Although it does not enter into the calculation of the color index, it is probably an important factor in explaining increasing or decreasing values of the color index in the various anemias.[5]

Data. One hundred treated cases of pernicious anemia, chosen at random, were divided into male and female series and such necessary calculations were made to give weekly averages of the results so that the individual error could be minimized. These cases were followed with daily blood counts for periods ranging from 2 to 4 weeks and then at frequent intervals for more than 1 year. There were 679 observations made. The red blood cell counts were made on a Neubauer-Levy counting chamber (new ruling, U. S. Bureau of Standards). The hemoglobin was calculated in a Sahli hemoglobinometer in the usual manner with $\frac{N}{10}$ hydrochloric acid, allowed to stand for 1 minute, diluted with distilled water, and compared with a colored glass rod standard. Cell measurements were made on all cases at the time of admission to the hospital and on many at the time of discharge. These measurements were made on Wright-stained cover slip preparations, with an eyepiece micrometer. (According to some observers this procedure is recognized as giving smaller diameters than the "wet" methods). The resulting figures were plotted on ruled paper for comparison with the normal Price-Jones curve.

TABLE 1.—AVERAGE COLOR INDEX IN 100 CASES OF PERNICIOUS ANEMIA ON ADMISSION AND A YEAR OR MORE AFTER EFFECTIVE TREATMENT.

Total cases, 100.	Total observations, 679.	Admission.		First week.		Second week.		Third week.		Fourth week.		Two months.		Three months.		Four months.		Five months.		Six months.		One year or more.	
		M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.
Male 64	Observations	124	67	60	33	56	31	40	19	43	19	43	20	22	15	12	7	15	7	13	6	18	9
	Highest color index	1.70	1.50	1.60	1.70	1.50	1.30	1.50	1.40	1.40	1.08	1.40	1.20	1.20	1.08	1.02	1.20	1.20	1.10	1.10	0.98	1.50	1.04
Female 36	Lowest color index	0.70	0.77	0.79	0.90	0.76	0.86	0.70	0.88	0.69	0.70	0.62	0.70	0.64	0.55	0.71	0.65	0.73	0.83	0.78	0.85	0.80	0.63
	Average color index	1.17	1.12	1.16	1.10	1.10	1.06	1.10	1.06	1.05	1.02	0.92	0.92	0.88	0.81	0.91	0.91	0.94	0.93	0.94	0.91	1.00	0.90

In analyzing the figures (Table 1 and Fig. 1) several important features present themselves. The average color index of the female series is always less than that of the male series, due probably to constitutional variations. It is also to be noted that the uncorrected color index falls below 1 at some time between 4 and 8 weeks after the onset of treatment, although individual readings may be above or below 1 at any time during complete relapse up to 1 year or more with treatment. Although the figures for each type of treatment have not been listed separately, it was observed that the color index was influenced in a like manner by liver, liver extract and ventriculin.

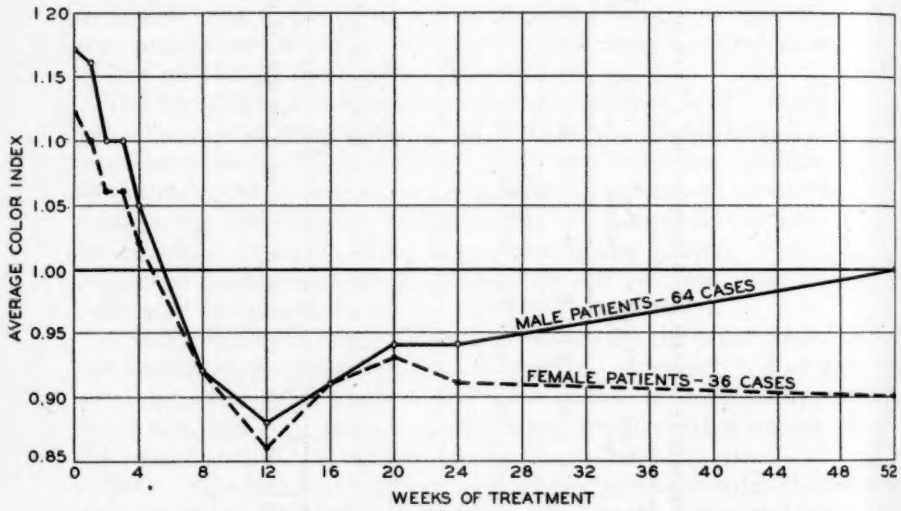

FIG. 1.—Effect on average color index with various types of adequate therapy in pernicious anemia. Five million R. B. C. per c.mm. and 14 gm. Hb. per 100 cc. regarded as 100 per cent.

In a comparison of the color index and the red blood cell count (Table 2) it was observed that the same variations exist in the individual values of the index, some readings being below 1, others above 1, regardless of the red blood cell count; however, the lower the red blood cell count, the higher was the color index average. As the arbitrary standard of normal for the red blood cells was approached, following treatment, the color index tended to approximate unity. Between the range of 4,000,000 and 5,000,000 red cells per c.mm. a level was reached at which the color index becomes 1 or less.

In 15 of the foregoing cases cell measurements were made on entrance (before treatment) and at discharge. The percentage of cells larger than 7.5 micra was estimated in each case and these results were plotted against the number of millions of red blood

cells. The results obtained substantiate the findings of Medearis and Minot.[6] As the blood picture approaches normal in treated cases, the percentage of extremely large cells diminishes in amount and returns to within the normal range (Fig. 2).

TABLE 2.—COLOR INDEX AS COMPARED WITH MILLIONS OF RED BLOOD CELLS FOLLOWING TREATMENT.

	Red blood cells in millions per c.mm.				
	0 to 1.	1 to 2.	2 to 3.	3 to 4.	4 to 5+.
Admission	1.15	1.12	1.15	1.01	0.93
1 week	1.26	1.16	1.10	1.03	0.89
2 weeks	..	1.07	1.07	1.09	0.95
3 weeks	1.10	1.21	1.07	1.04	0.93
4 weeks	..	1.23	1.08	1.03	0.88
8 weeks	..	..	1.04	0.97	0.87
12 weeks	..	..	..	1.01	0.86
16 weeks	..	..	..	0.97	0.89
20 weeks	..	..	..	1.06	0.91
24 weeks	..	..	..	0.92	0.93
52 weeks	..	..	..	1.10	0.91

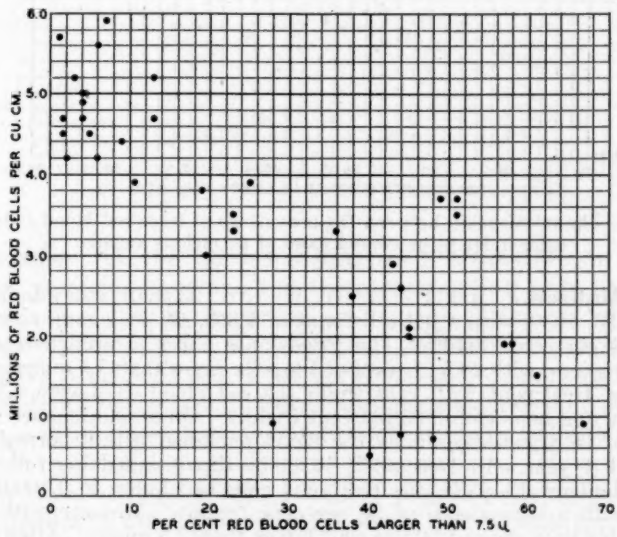

FIG. 2.—The relationship of the percentage of large red blood cells and red blood cell count in treated cases of pernicious anemia.

When the percentage of cells larger than 7.5 micra in untreated cases is plotted against the red blood cell count at the time of entrance (Fig. 3) there appears to be no simple relationship. It is interesting to note, however, that regardless of whether a patient is just beginning to relapse or has a severe anemia, the large cells are very much in evidence. This is probably one of the very earliest changes in the blood. Since, in cases sufficiently treated, the percentage of large cells varies directly with the degree of the

anemia,[6] being within the range of normal when a mild anemia is present; and since in untreated cases the percentage of large cells is increased, regardless of the severity of the anemia, this factor may be used as a differential point to note whether a patient is beginning to relapse or not.

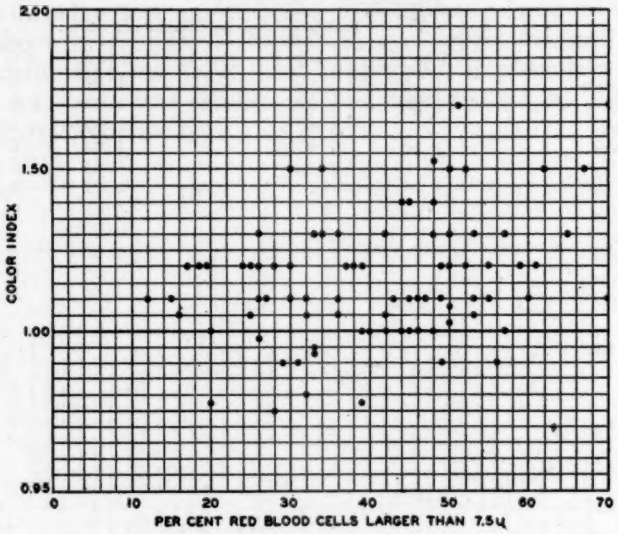

FIG. 3.—The relationship between the percentage of large red blood cells and color index in untreated cases of pernicious anemia.

Case Abstracts. CASE 1.—Mr. W. W. (No. 233360) was admitted on January 23, 1930, with a red cell count of 1,800,000 per c.mm. and hemoglobin 44 per cent (Sahli). The Price-Jones curve showed a secondary peak at 9 micra, with 28.5 per cent of the cells larger than 7.5 micra. After 2 months' treatment with ventriculin the red blood cells were 4,300,000 per c.mm. and hemoglobin 85 per cent (Sahli). On a maintenance dose of 50 gm. of ventriculin per week the blood remained within normal limits for about 1 year. In December, 1930, he discontinued his full dosage and by January 12, 1931, the red blood cells had fallen to 3,100,000 per c.mm., with a hemoglobin of 80 per cent (Sahli). Measurement of the cells at this time showed 30 per cent larger than 7.5 micra. After careful questioning of the patient no symptoms of relapse were elicited. With the laboratory findings a definite diagnosis of pernicious anemia in early relapse could be made.

This case illustrates the presence of large cells in greatly increased numbers early in relapse. Their presence becomes a valuable diagnostic point when one considers a patient with a count of 4,000,000 red cells per c.mm., with adequate treatment, and a similar count in a patient with inadequate treatment. In the former case the percentage of cells larger than 7.5 micra will be less than 5 per cent, whereas in the latter the percentage will range from 20 to 30 per cent. This factor will serve as a valuable differential

feature in the diagnosis of pernicious anemia when the red blood cell count is around 4,000,000 per c.mm., and is present even in the absence of an increased bilirubinemia and when the degree of poikilocytosis is too small to aid in the diagnosis.

In Fig. 4 the percentage of cells larger than 7.5 micra is plotted against the color index in untreated cases. From this, it can be seen that there is no definite correlation between the two. Nevertheless, it is noted that with a high color index the percentage of cells larger than 7.5 micra is greatly increased.

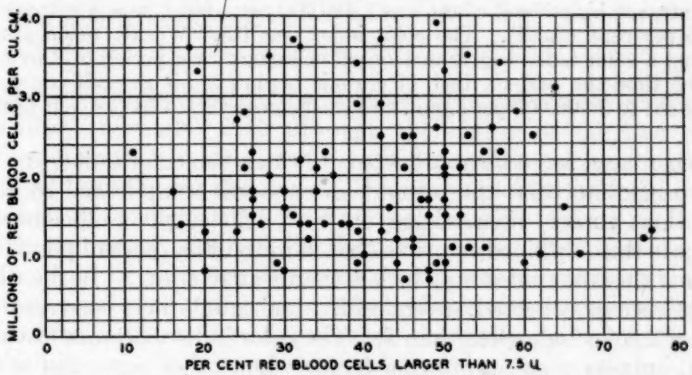

FIG. 4.—The relationship of the percentage of large red blood cells and red blood cell count in untreated cases of pernicious anemia.

Discussion. Of the various criteria used in the differential diagnosis of pernicious anemia, the three outstanding tests have been the absence of free hydrochloric acid in the gastric secretion, the high color index and the macrocytosis. Within the past few years there have been published a few series of cases demonstrating that practically all patients with pernicious anemia have no free hydrochloric acid in their gastric contents; occasionally an isolated case has been reported contradictory to these findings. However, none of these cases have ever been definitely proven as being true pernicious anemia at autopsy. Sturgis[7] states that at one time it was generally accepted that gastric anacidity and a high color index were the two most constant features in pernicious anemia. According to Haden,[5] "A color index greater than 1, when correctly determined, is usually regarded as the most constant and characteristic blood finding in pernicious anemia." Recently there have been observed a few cases of pernicious anemia complicated by hemorrhage, tumors, chronic infections, glandular dystrophies, or a food deficiency, which gave a color index of a secondary anemia rather than a primary anemia. These cases had most of the characteristics of pernicious anemia and responded in the usual manner to the treatment for this disease.

CASE 2.—Mrs. A. B. (No. 2066267) had pernicious anemia and a pelvic tumor. The Price-Jones curve of red blood cell measurement showed a secondary peak at 8.2 micra, with 14 per cent of the cells larger than 7.5 micra. There was also another peak at 6.3 micra, which was suggestive of a secondary anemia. Her reticulocyte rise reached a maximum of 35 per cent in 7 days, but at no time was her color index more than 1. It varied as follows: On admission, 0.83; 1 week after treatment, 0.81; 2 weeks after treatment, 0.75; 1 year after treatment, 0.63.

CASE 3.—Mr. P. (No. 215315) had pernicious anemia complicated by chronic nephritis. His Price-Jones curve showed 23.5 per cent cells larger than 7.5 micra and 64 per cent smaller. With liver extract he had a characteristic rise of reticulocytes, reaching a maximum of 27.5 per cent. On entrance his red cell count was 1,480,000 per c.mm., with a hemoglobin of 15 per cent (Sahli). The color index was 0.5. Weekly blood studies showed a color index less than 1 on all occasions for a period of 2 months. At the time the patient died, of chronic nephritis, his red cell count had increased to 3,900,000 per c.mm. and the hemoglobin to 54 per cent (Sahli).

Other cases have been collected in which the color index was low due to the fact that the primary disease was complicated by some infection, tumor, hemorrhage or food deficiency. Sufficient evidence is thus obtained to prove that in individual cases of pernicious anemia the color index may be less than 1 at all times. In the whole series of cases collected, several individual counts have been recorded giving a color index less than 1. The color index becomes of value, then, only as a substantiating factor when other signs and symptoms of pernicious anemia are present. Further, if the color index is always less than 1 and the diagnosis of pernicious anemia is definitely established, there must be present some complicating factor.

It is possible now to answer the original question as to the clinical value of the uncorrected color index in the diagnosis of pernicious anemia. One reading in itself is of little value, for the reading may or may not be above 1. However, over a period of time, with several readings, its importance is well appreciated. Individual readings above 1 are not pathognomonic of pernicious anemia, but serial readings may be used as substantiating evidence.

Regardless of the indices used or the "absolute cell determinations," a standard must be employed. Since it is physically impossible to establish a normal on account of such factors as time, age, sex, race, climate, season, digestion, dehydration, water administration, diet, pregnancy and lactation, menstruation, vasomotor and psychomotor influences,[8] all results have significance. One method or another may be more accurate as a laboratory procedure, but this is usually accomplished at the sacrifice of simplicity.

The normal standards for the various chemical constituents of the blood, such as sugar, bilirubin, chlorids, calcium, phosphorus and the like, are not "single figures," but comparatively wide ranges. The possibility of a single figure for any of these normals was ruled out when contributory factors were considered. For

similar reasons it would be better to consider the normal hemoglobin content of the blood as from 14 to 16 gm. per 100 cc.

The question might arise as to the difference in the results if 16 gm. of hemoglobin per 100 cc. of blood were used instead of 14 gm. as a standard for the calculation of the color index. The following table shows the difference in per cent reading of the two standards:

14 grams.	16 grams.
100	88
75	66
50	44
25	22

There exists a constant factor as a difference between the two so-called "normals" and although the higher of the two would reduce the numerical values of the color index somewhat, the general results would remain the same. The curves plotted from the results given in this paper would have almost a duplicate form at slightly lower numerical values. Further, the lower the percentage of hemoglobin, or the more severe the anemia, the closer the two values approximate each other, and, since the error in the method of estimation is about 3 to 5 per cent, the difference would become negligible.

Macrocytosis, although a constant feature in the blood picture of pernicious anemia in relapse, may occur in other anemias, as those produced by cancer metastasis to the bone marrow, sprue, fish tapeworm and certain lesions of the liver and pancreas. Cell size alone cannot be used as pathognomonic evidence in any anemia, hence its value is limited. However, the absence of macrocytosis in a patient with anemia makes the diagnosis of pernicious anemia highly improbable.

Conclusions. 1. The uncorrected color index represents the actual hemoglobin per cent reading (100 per cent as normal), over the percentage of red blood cells (5,000,000 being equivalent to 100 per cent), disregarding such factors as sex and the various hemoglobin standards.

2. Because of the wide range of normal red blood cell counts, 5,000,000 cells per c.mm. may be used as an average arbitrary standard. From 14 to 16 gm. of hemoglobin per 100 cc. of blood are suggested as a standard of normal.

3. The average and serial color indexes in uncomplicated cases of pernicious anemia are above 1 before treatment; those of the male series are higher than those of the female.

4. Regardless of type of effective treatment, the influence on the color index is the same; the average and serial color indexes remain above 1 for about 6 weeks after treatment is started, then become less than 1.

5. In untreated and uncomplicated cases the lower the initial red blood cell count the higher the average color index. As the red cell count approaches the arbitrary normal following adequate treatment, the color index tends to approximate unity. Within the range of 4,000,000 to 5,000,000 red blood cells per c.mm. a level is reached at which the color index becomes 1 or less.

6. A single color index determination is not always diagnostic in cases of pernicious anemia, as individual readings may be above or below 1; but during relapse the average color index is always above 1 unless some complication is present.

7. The color index may be influenced by such complications as hemorrhage, chronic infections, glandular dystrophies and food deficiencies.

8. The increase in the percentage of red blood cells larger than 7.5 micra in early relapse, regardless of the severity of the anemia, may be used as a factor differentiating pernicious anemia from secondary anemia.

9. In untreated cases of pernicious anemia a high color index is always associated with a marked increase in the percentage of cells larger than 7.5 micra.

10. The presence of increased numbers of large cells in a blood film, regardless of the red blood cell count, is one of the earliest and most constant findings of the blood in beginning relapse in pernicious anemia.

BIBLIOGRAPHY.

1. Haden, R. L.: The Volume and Hemoglobin Content of the Erythrocytes in Health and Disease, Folia hæmatol., 1925, **31**, 113.

2. Van Slyke, D. D., and Neill, J. M.: Determinations of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, J. Biol. Chem., 1924, **61**, 523.

3. Osgood, E. E.: Hemoglobin, Color Index, Saturation Index and Volume Index Standards: Redeterminations Based on Findings in 139 Healthy Young Men, Arch. Int. Med., 1926, **37**, 685.

4. Wintrobe, M. M.: Volume and Hemoglobin Content of Red Corpuscle: Simple Method of Calculation, Normal Findings and Value of Such Calculations in Anemias, Am. J. Med. Sci., 1929, **177**, 513.

5. Haden, R. L.: Value of Volume Index in Diagnosis of Pernicious Anemia, J. Am. Med. Assn., 1924, **73**, 671.

6. Price-Jones, C.: Diameters of Red Cells in Pernicious Anemia and in Anemia Following Hemorrhage, J. Path. and Bact., 1922, **25**, 487; Red Cell Diameters in 100 Healthy Persons and in Pernicious Anemia: Effect of Liver Treatment, J. Path. and Bact., 1929, **32**, 479; The Variation in the Sizes of Red Blood Cells, Brit. Med. J., 1910, **2**, 1418. Medearis, D. M., and Minot, G. R.: Studies on Red Blood Cell's Diameter: In Pernicious Anemia, Before and During Marked Remission, and in Myelogenous Leukemia, J. Clin. Invest., 1927, **3**, 541. Bell, J. R., Thomas, F. K., and Means, J. H.: Studies on Red Cell Diameter: In Health and in Pernicious Anemia, J. Clin. Invest., 1926, **3**, 229. Persons, E. L.: Studies on Red Blood Cell Diameter: Relative Diameter of Immature (Reticulocytes) and Adult Red Blood Cells in Health and Anemia, Especially in Pernicious Anemia, J. Clin. Invest., 1929, **7**, 615. Grosh, L. C., and Stifel, T. L.: Diameter of Red Blood Cells in Differentiation of Anemias, Arch. Int. Med., 1925, **36**, 874.

7. Sturgis, C. C.: Personal Communication.

8. Wintrobe, M. M.: The Erythrocyte in Man, Medicine, 1930, **9**, 195.

STUDIES OF ANEMIA IN PREGNANCY.

I. Gastric Secretion in Pregnancy and the Puerperium.

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Recent studies have again emphasized the significance of disturbances of the gastro-intestinal tract in the pathogenesis of remote and systemic conditions.[1,2] The pathogenesis of certain cases of deficiency disease has been found by many workers to lie in part in disordered intestinal conditions. The work of Castle and his associates[3] has indicated that the absence from the gastric secretions of a ferment-like substance is the main etiologic factor in the development of Addisonian pernicious anemia. Recently Keefer, Yang and Huang[4] have observed the influence of prolonged diarrhea in the production of disturbances of nutrition and blood formation, and Eusterman and O'Leary[5] have noted the effects of gastro-intestinal lesions in the etiology of certain cases of pellagra. The work of Mettier and Minot[6] suggests that the hydrogen-ion activity of the upper intestinal tract may be of great importance in the absorption or utilization of materials necessary for blood formation.

These observations suggested to us that the study of the gastric secretions during the normal physiologic process of pregnancy might be of aid in determining the etiologic factors involved in the common anemias of pregnancy. Study of the gastric secretions rather than of other measures of gastro-intestinal function was made because of the relative ease of securing repeated observations on the same individuals and because of the apparent importance of these secretions in the pathogenesis of certain disturbances of blood formation not associated with pregnancy.

In this report only data on the gastric secretions will be presented; studies correlating hematopoiesis in the same individuals will be the subject of a separate communication.

Literature. The few studies of gastric secretion during pregnancy that have been made are uniform in indicating a high incidence of diminished and absent free HCl. In none of these studies has histamin been employed when the usual test meal failed to stimulate the secretion of free HCl. Nakai,[7] in 1925, reported the results of single gastric analyses on each of 14 pregnant women, in which he

found an average free acidity of 22 cc. N/10 acid per 100 cc. during the first half of pregnancy and 27 cc. during the last half, as compared to an average of 31 cc. found by other Japanese investigators in nonpregnant women. Arzt,[8] employing a test meal of shredded wheat and water, during the first trimester of pregnancy, found gastric anacidity in 5 patients, and an average of 11 cc. in 13 others. In 6 patients observed during the last half of pregnancy he found an average free acidity of 15 cc. In a subsequent study[9] he found 29 of 50 patients lacking free HCl during the first trimester of pregnancy, 6 of whom reëxamined in the last trimester of pregnancy averaged 11 cc. Recently Mason[10] reported 4 patients with gastric anacidity and 2 with an average of 8 cc. during the first trimester of pregnancy.

Methods of Investigation. Following preliminary observations of secretory changes during pregnancy, 24 apparently normal women who reported for routine prenatal care were selected for study. They ranged in age from 20 to 36 years (average, 27.6 years). Five were primiparæ; 1 was pregnant for the fourteenth time; the average number of pregnancies was 4 per patient. Gastric analyses were performed at approximately monthly intervals during gestation and again 7 to 10 days after delivery. A gastroduodenal catheter with an external diameter of 4 mm. was uniformly employed, as producing less gagging than tubes with metal bulbs. All patients had abstained from food for 12 hours before examination. The tube, lubricated with mineral oil, was passed to the fundus of the stomach, the fasting contents removed, 50 cc. of 7 per cent ethyl alcohol instilled and extraction undertaken 20 and 40 minutes later. If no free HCl could be detected by Töpfer's reagent in any of the 3 specimens, 0.3 mg.* of histamin hydrochlorid was then injected subcutaneously and extractions of gastric secretion made 20 and 40 minutes later.

Alcohol was used routinely because of its freedom from the buffer action of the older type of test meals. It has been noted that the acidity of specimens following the alcohol test meal is generally the same as or higher than those of bread or biscuit and water meals. As histamin, even in these small doses, is a more powerful stimulant than alcohol, its employment was limited to such patients as failed to secrete HCl after the alcohol test meal. In the histamin tests free HCl was either completely absent or present in subnormal amounts.

In all, 142 gastric analyses were performed on the 24 patients. The quantity, character, hydrogen-ion activity, free HCl and total acidity of all specimens were determined. The pepsin content of the highest acid secretion was estimated by the method of Mett.[12] (The gastric juice was diluted with an equal quantity of water and titrated to pH 1.4.) Free and total acidity were titrated with Töpfer's solution and phenolphthalein, respectively. Hydrogen-ion activity was determined colorimetrically with Clark and Lub's indicators.[13]

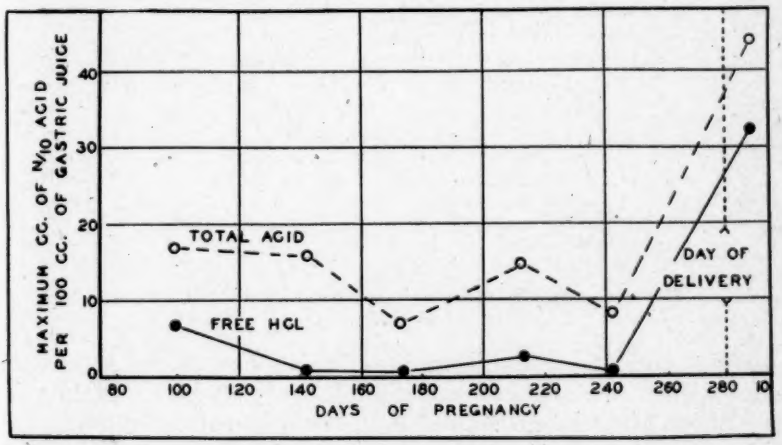
Results. In 18 gastric analyses performed by the same technique on nonpregnant women the maximum free-acid concentration varied from 19 to 76 cc. N/10 acid per 100 cc. of gastric juice, with an

* Gompertz and Cohen[11] have shown that 0.25 mg. of histamin is entirely adequate to provoke a typical acid secretion, and its administration is not accompanied by as undesirable symptoms as the larger doses.

average of 38 cc. The peptic activity varied from 15 to 20 mm. digestion of egg albumen per day. Carlson[14] gives the composition of normal human gastric juice as containing from 40 to 50 cc. N/10 acid per 100 cc. Bloomfield and Keefer[15] have noted the constancy of acid secretion during repeated analyses in the same individual under basal conditions, using the same test stimulus.

Eighteen of the 24 patients showed acid secretion below the normal range during most of the period of gestation. The 24 patients were divided into four groups, according to the degree of reduction of acidity. The first group consisted of 3 patients who had a total and persistent post-histamin achlorhydria with no return of free acid after delivery. The maximum hydrogen-ion activity after histamin in this group was pH 7. Peptic activity of these patients' gastric juice was of a low order, averaging 3.3 mm. digestion of egg albumen per day.

CHART I.—GASTRIC SECRETIONS OF PATIENT 3.*



In the second group were 7 patients who during most of pregnancy secreted gastric juice with a free HCl concentration of less than 10 cc. N/10 acid per 100 cc. after an alcohol test meal. The average maximum was 3.3 cc., with an average total acidity of 12 cc. and an average peptic activity of 6.8 mm. per day. Five of these patients on 18 analyses secreted no free HCl until after histamin had been injected, and 3 secreted no acid after histamin on one or more occasions. Of these 7, 2 showed a return to normal acid secretion and 3 secreted increased, although still subnormal, amounts

* Maximum free HCl and total acidity after alcohol test meals. Following subcutaneous injection of 0.3 mg. histamin, 44, 38 and 26 cc. of N/10 free HCl per 100 cc. of gastric juice were present on the 142d, 177th and 244th days, respectively, when no free HCl was found after alcohol test meals. (In this and subsequent charts the day of delivery is arbitrarily set at 280.)

of acid after delivery. The analyses of Patient 3 (Table 1, Chart I) illustrate the secretions of a case typical of this group. For simplicity in presentation, only the maximum values obtained in any single gastric analysis are shown.

TABLE 1.—TYPES OF GASTRIC SECRETORY RESPONSE DURING PREGNANCY.

Patient No.	Day of pregnancy.	Maximum free HCl. (Within 40 min. of alcohol test meal, cc. N/10 acid per 100 cc.)	Maximum total acidity. (Within 40 min. of alcohol test meal, cc. N/10 acid per 100 cc.)	Maximum H^+ ion activity, pH.	Pepsin, mm. of egg albumen digested per day.
3	100	7.0	17.0	2.4	8.0
	142	0.0*	16.0	5.8	8.0
	177	0.0*	7.5	6.0	4.0
	214	2.5	14.5	2.8	5.2
	244	0.0*	8.0	5.4	3.6
	Post-partum 8	32.0	44.0	1.4	7.8
4	103	21.0	50.0	1.8	5.6
	141	11.5	19.5	2.0	6.0
	208	12.0	23.0	1.8	9.0
	243	27.0	33.5	1.4	10.5
	Post-partum 10	44.0	52.0	1.4	18.0
2	79	45.0	52.5	1.4	7.5
	112	60.0	73.0	1.4	14.0
	143	49.0	63.0	1.4	12.0
	171	50.0	74.0	1.4	19.0
	201	36.0	41.0	1.4	14.0
	227	36.5	46.5	1.4	13.5
	253	84.0	98.0	1.4	16.0
	Post-partum 10	89.0	97.0	1.4	23.0

* Free HCl was present in the gastric secretions of this patient on these three occasions following the injection of histamin.

Eight patients, comprising the third group, secreted gastric juice with a free acid concentration of less than 20 cc. N/10 acid per 100 cc. after the alcohol test meal throughout most of the period of pregnancy. Their average maximum free HCl was 17.8 cc., average maximum total acidity 26.7 cc. and peptic activity 9 mm. per day. Seven of these 8 patients secreted normal amounts of free acid within 10 days after parturition. Analyses of Patient 4 (Table 1, Chart II) illustrate the gastric secretions of a patient characteristic of this group.

The remaining 6 patients, classed in the fourth group, secreted gastric juice after the alcohol meal which was within normal range throughout pregnancy, with an average maximum free HCl of 34.5 cc. N/10 acid per 100 cc., an average maximum total acidity of 45.9 cc. and an average peptic activity of 11 mm. digestion per day. After delivery 5 of these 6 patients showed definitely increased gastric acidity with free HCl, varying from 50 to 90 cc. and averaging 71.4. Patient 2 (Table 1, Chart III) is a typical example of this group.

Seventeen of the 21 patients who did not have persistent anacidity secreted much greater amounts of acid after delivery than they had

CHART II.—GASTRIC SECRETIONS OF PATIENT 4, FOLLOWING ALCOHOL TEST MEALS.

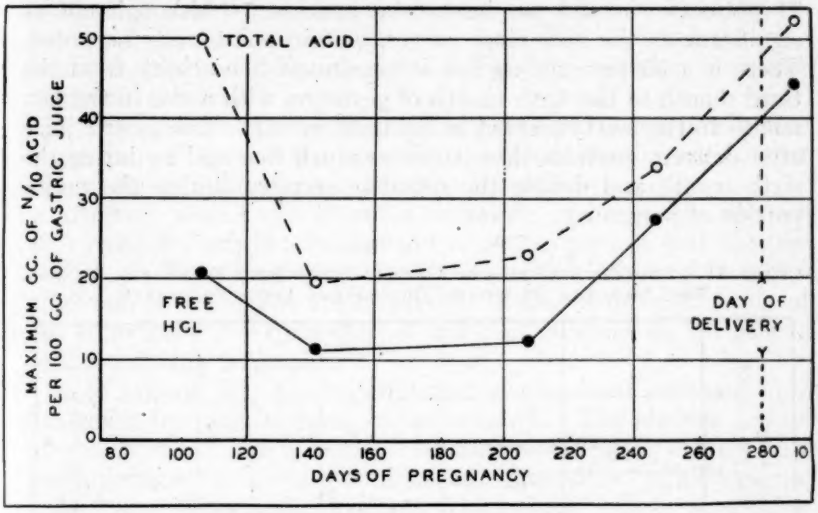
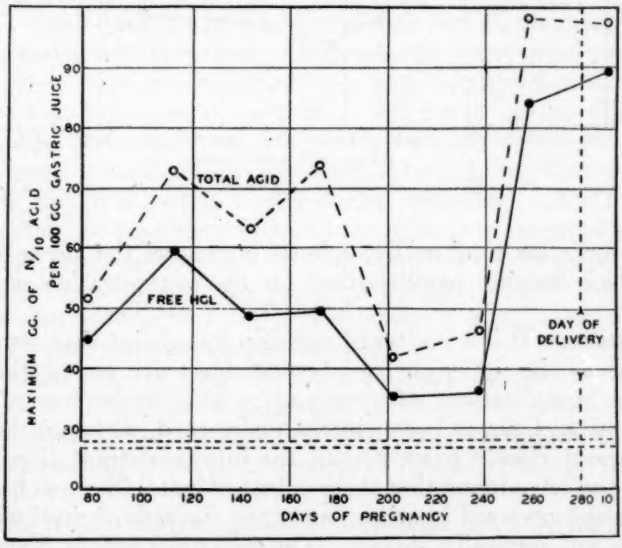


CHART III.—GASTRIC SECRETIONS OF PATIENT 2, FOLLOWING ALCOHOL TEST MEALS.

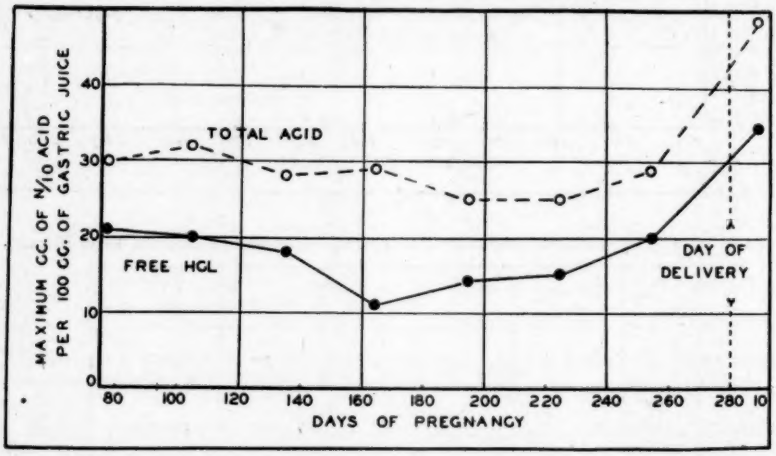


during pregnancy. Since these women were not studied before pregnancy, the condition after pregnancy has been taken as *probably* representative of the gastric secretion before pregnancy. In a few

cases normal acid values were noted early in pregnancy and a number showed a tendency to secrete more acid in the last month than in the earlier months of gestation (Charts II and III).

A composite curve is shown in Chart IV, giving the data for the 21 patients who did not have total anacidity. Although not as significant as the individual curves, certain points may be noted. There is a 50 per cent decline in maximum free acidity from the third month to the sixth month of gestation with a rise in the last month to the level observed in the third month. The gastric juice after delivery contains three times as much free acid as during the sixth month and double the quantity secreted during the major portion of pregnancy.

CHART IV.—COMPOSITE CURVE OF GASTRIC SECRETIONS FOLLOWING ALCOHOL TEST MEALS OF 21 WOMEN DURING AND AFTER PREGNANCY.



The curve for total acidity follows in general the curve for free acid which roughly parallels that for the concentration of peptic enzyme.

Discussion. It is a matter of common knowledge that symptoms referable to the upper gastro-intestinal tract are among the most frequent complications of pregnancy. The mechanism of these conditions has never been clearly understood, although recently Alvarez and Hosoi[16] have studied the intestinal tract of pregnant rabbits and have found that the gradient of irritability was flattened in some and reversed in others, and that the rate of rhythmic contraction was generally slowed. The investigations of Nakai and Arzt previously mentioned, together with the data here presented, indicate that there is a decreased secretory power of the gastric mucosa during pregnancy. The nature of the mechanism respons-

ible for this diminution remains obscure. In the nonpregnant individual it is known that fever,[17] injections of foreign protein[18] and artificial tropical climate[19] will depress gastric function. A group of investigators in India[20] has compared the *fasting* gastric contents of vegetarian Hindus and of meat-eaters, without detecting any difference between the two. Low chlorid diets have been found to have no influence upon the gastric secretion until late stages of inanition.[14]

In our studies no correlation could be obtained between reduction in gastric acidity and the age of the patients, nor did the number of previous pregnancies appear to be of significance.

Although mucus can diminish titratable free acid, the absence of correlation between the amount of mucus present and the free acidity of the specimens, together with the low total acidities observed, indicate that mucus played no rôle in the production of the abnormally low quantities of free acid observed in the gastric contents during pregnancy.

It is known that the regurgitation of duodenal contents may neutralize free acid secreted in the stomach. The absence of bile in almost all of the specimens obtained is evidence against this being a factor in the results observed. Moreover, peptic enzyme values were fairly well correlated with acidity values, suggesting that neutralization from either duodenal contents or mucus was not involved.

From these data it appears that a majority of pregnant women have a significant reduction in the free HCl and total acidity of their gastric juice, accompanied by a parallel reduction in ferment content and hydrogen-ion activity. All but 1 of the 6 patients who had an apparently normal gastric juice during pregnancy had an increased gastric acidity post-partum, suggesting that they also had a reduction of gastric acidity during pregnancy. It is apparent that, unlike the constancy of gastric secretions in repeated analyses upon the same subject noted in nonpregnant individuals,[15] wide variations occur during the course of pregnancy. No correlation between these variations and either morning sickness or vomiting late in pregnancy could be determined.

The importance of altered gastric function that occurs in pregnancy is a matter for consideration from various points of view. Its rôle in inhibiting optimal nutrition may be important, also its possible relation to blood formation as discussed in the following paper.

Summary. 1. Gastric analyses (142) made upon 24 women during pregnancy and the puerperium showed that 75 per cent of the patients did not secrete normal amounts of free HCl or pepsin during more than half of the period of pregnancy.

2. Excluding 3 patients who had persistent achlorhydria even

after histamin injection, 80 per cent of the patients secreted higher concentrations of HCl in the gastric juice after delivery than during pregnancy; the secretion during the puerperium being approximately 3 times as great as that during the sixth month of gestation.

It is a pleasure to acknowledge our indebtedness to the visiting surgeons and house staff of the Obstetrical Service of the Boston City Hospital, through whose coöperation this study was made possible.

BIBLIOGRAPHY.

1. Castle, W. B., Heath, C. W., Strauss, M. B., and Townsend, W. C.: The Relationship of Disorders of the Digestive Tract to Anemia, J. Am. Med. Assn., 1931, **97**, 904.

2. Eggleston, E. L.: Pathologic Conditions Secondary to Achlorhydria, J. Am. Med. Assn., 1931, **97**, 1216.

3. Castle, W. B., Heath, C. W., and Strauss, M. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: IV. A Biologic Assay of the Gastric Secretion of Patients with Pernicious Anemia and Free Hydrochloric Acid and that of Patients without Anemia or with Hypochromic Anemia Having No Free Hydrochloric Acid, and of the Rôle of Intestinal Impermeability to Hematopoietic Substances in Pernicious Anemia, Am. J. Med. Sci., 1931, **182**, 741.

4. Keefer, C. S., Yang, C. S., and Huang, K. K.: Anemia Associated with Chronic Dysentery, Arch. Int. Med., 1931, **47**, 436.

5. Eusterman, G. B., and O'Leary, P. A.: Pellagra Secondary to Benign and Carcinomatous Lesions and Dysfunction of the Gastro-intestinal Tract, Arch. Int. Med., 1931, **47**, 633.

6. Mettier, S. R., and Minot, G. R.: The Effect of Iron on Blood Formation as Influenced by Changing the Acidity of the Gastroduodenal Contents in Certain Cases of Anemia, Am. J. Med. Sci., 1931, **181**, 25.

7. Nakai, T.: On the Gastric Juice of the Pregnant Woman, Tokio J. Biochem., 1925, **5**, 465.

8. Arzt, F.: On the Gastric Juice During Pregnancy, Am. J. Obst. and Gynec., 1926, **12**, 879.

9. Idem: Further Observations on the Gastric Juice in Pregnancy, Ibid., 1930, **20**, 382.

10. Mason, L. W.: Gastric Acidity in Pregnancy, Colorado Med., 1931, **28**, 392.

11. Gompertz, L. M., and Cohen, W.: The Effect of Smaller Doses of Histamin in Stimulating Human Gastric Secretion, Am. J. Med. Sci., 1929, **177**, 59.

12. Hammarsten, O., and Hedin, S. G.: A Textbook of Physiological Chemistry, New York, John Wiley & Sons, 1914.

13. Clark, W. M.: The Determination of Hydrogen Ions, Baltimore, The Williams & Wilkins Company, 1923.

14. Carlson, A. J.: The Secretion of Gastric Juice in Health and Disease, Physiol. Rev., 1923, **3**, 1.

15. Bloomfield, A. L., and Keefer, C. S.: Clinical Physiology of the Stomach, Arch. Int. Med., 1926, **38**, 145.

16. Alvarez, W. C., and Hosoi, K.: Reversed Gradients in Bowel of Pregnant Animals, Am. J. Obst. and Gynec., 1930, **19**, 35.

17. Meyer, J., Cohen, S. J., and Carlson, A. J.: Contribution to the Physiology of the Stomach: XLVI. Gastric Secretion during Fever, Arch. Int. Med., 1918, **21**, 354.

18. Meyer, J., and Kartoon, L. B.: The Effects of Intravenous Injections of Foreign Protein on Peptic Ulcer, Arch. Int. Med., 1930, **46**, 768.

19. Borchardt, W.: Die Magenfunktion im künstlichen Tropenklima (Nach Versuchen an Tieren und Menschen), Klin. Wchnschr., 1930, **9**, 886.

20. Bhatia, S. L., Patel, H. S., and Dundas, J. D.: Studies in Gastric Secretion, Part I, Ind. J. Med. Res., 1931, **19**, 259.

STUDIES OF ANEMIA IN PREGNANCY.

II. The Relationship of Dietary Deficiency and Gastric Secretion to Blood Formation During Pregnancy.

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The occurrence of anemia during the progress of pregnancy has long been a matter of common observation. Bland, Goldstein and First[1] have recently reviewed the literature and published a bibliography of 56 references up to 1929. Since then several other papers have appeared.[2-10] A survey of the literature suggests a number of hypothetic causes of this anemia, but fails to reveal evidence confirming any one of them. It has been well established that the anemia is most marked in the early part of the last trimester of pregnancy, and that there is some slight tendency to spontaneous recovery in the last month or two immediately preceding delivery. The absence of correlation between the degree of the anemia and the age, parity or blood pressure of the patients has been noted.[1] Focal infection, toxemia and syphilis have not been found to play a significant rôle.[1]

In the absence of a satisfactory explanation for the reduction in both erythrocytes and hemoglobin these phenomena have been termed "physiologic anemia of pregnancy" and considered normal. Marked degrees of this physiologic anemia of pregnancy resemble the anemias associated with gastro-intestinal disturbances, poor diet and chronic blood loss. An investigation of these three factors in 22 pregnant women without demonstrable disease, who applied for routine prenatal care, was, therefore, made in order to throw light upon the mechanism of anemia in pregnancy.

Methods. Complete measurement of gastro-intestinal function should include a study, not only of the contents, but also of all of the known enzymes, and those of the accessory glandular organs, as well as observations on the absorptive capacity and motility of the bowel. The difficulty of such a task led us to choose a measure of gastric secretory function which could easily be determined at monthly intervals and might serve as an index of general gastro-intestinal function, namely, the ability of the stomach to secrete acid. Previous studies[11] have shown that, while defects of gastric secretion may occasionally be present without disturbance of acid secretion, in general a fair degree of correlation exists between the latter and other gastric secretory functions. Gastric analyses were performed at monthly intervals and after delivery as described in the preceding paper.[12]

The determination of a patient's diet over a period of years requires painstaking inquiry, but it was found possible to formulate a fairly definite concept of the patient's dietary habits from repeated and careful questioning. Careful histories were taken of the usual food intake of these patients for the years before and during pregnancy, and notes made of any disturbances during pregnancy, such as nausea or vomiting, which might interfere with the diet, either as to quality or quantity. The diets of none of the 22 patients were found defective in total calories, as evidenced by the description of the diets themselves and as inferred from the normal gain in weight exhibited by all. In no instance was there any apparent fat, carbohydrate or vitamin deficiency. Wide variations, however, occurred in the consumption of protein foods, fruits and green vegetables. The range extended from 1 patient who ate no meat, fish or eggs throughout pregnancy, and fruit and vegetables not more than once a week during and before pregnancy, to a patient who ate meat, fruit, vegetables and eggs twice daily. For purposes of classification, any patient who ate meat, fruit and vegetables less than three times a week was considered to have a poor diet, and the remainder considered to have a reasonably suitable diet, although probably few partook of diets that could be considered optimal. Most of these individuals ate meat, fruit and a vegetable at least once daily. The outstanding characteristic of the poor diets was the lack of iron and related mineral salts and the low protein intake.

To eliminate the effects of blood loss no patient giving a history of hemorrhage of any kind or menorrhagia was studied. However, since the fetal blood and muscle pigment-building materials are derived entirely from the maternal organism, it is conceivable that repeated pregnancies might produce the same effects as chronic blood loss. While it is possible also that the normal bleeding at delivery, if repeated many times, might represent chronic blood loss. Yet, if either of these possibilities is true there should be some correlation between the blood level and the number of pregnancies.

The blood was examined every month until the last month of pregnancy, then every 2 weeks until delivery, and on the first day after delivery, on the fifth or sixth, on the eighth to tenth day, and again 3 months after parturition. All determinations were made upon venous blood uniformly drawn without stasis from the antecubital vein. The diluting pipettes and counting chambers used were certified by the U. S. Bureau of Standards. The hemoglobin was determined by the Sahli method, with tubes calibrated so that 100 per cent equalled 15.6 grams of hemoglobin per 100 cc. of blood.

To determine the average ranges of the hemoglobin and erythrocyte concentration during and after pregnancy, and to furnish sufficient data to correlate blood levels with age and parity of the patients, 200 blood examinations were made upon an unselected group of 200 pregnant women, distributed equally in the last 8 months of pregnancy, 1 and 10 days postpartum.

Results. Two of the patients who were followed throughout pregnancy were definitely anemic when first seen. The remaining 20 were divided into four groups. The patients of the first three groups all had good diets.

Nine patients composed the first group and had throughout pregnancy 15 cc. or more N/10 free HCl per 100 cc. of gastric juice.[12] The 3 patients in the second group had less than this amount, and the 3 in the third group had total achlorhydria (*i. e.*, after injection of histamin). There were 5 patients in the fourth group, all of

whom had poor diets and less than 15 cc. of N/10 free HCl per 100 cc. of gastric juice.

The hemoglobin determinations on Group I, comprising the 9 patients whose gastric secretion contain 15 cc. or more N/10 HCl throughout most of pregnancy and who ate adequate diets, are shown in Chart I. Only 1 of these patients had below 60 per cent of hemoglobin at any time during pregnancy. The average difference between the highest and lowest determination in any month in this group was less than 14 per cent. Within 10 days after delivery all but 1 patient had between 73 and 84 per cent of hemoglobin. No significant change was found 3 months later. The average hemoglobin curve for this group (Chart IV) showed a 5 per cent loss from the third month of pregnancy to the tenth day post-partum.

Chart II represents the hemoglobin determinations on the second group composed of the 3 patients with less than 15 cc. of N/10 free HCl who had satisfactory diets. One of these patients had had an exceptionally good diet* throughout pregnancy and showed a hemoglobin curve which corresponded to the curves of the first group. The other 2, who took the average diet, had hemoglobins of 63 and 70 per cent, respectively, 10 days post-partum. Both had below 60 per cent during part or all of the third trimester of pregnancy. An average loss of 9 per cent hemoglobin occurred between the third month of pregnancy and the tenth day post-partum.

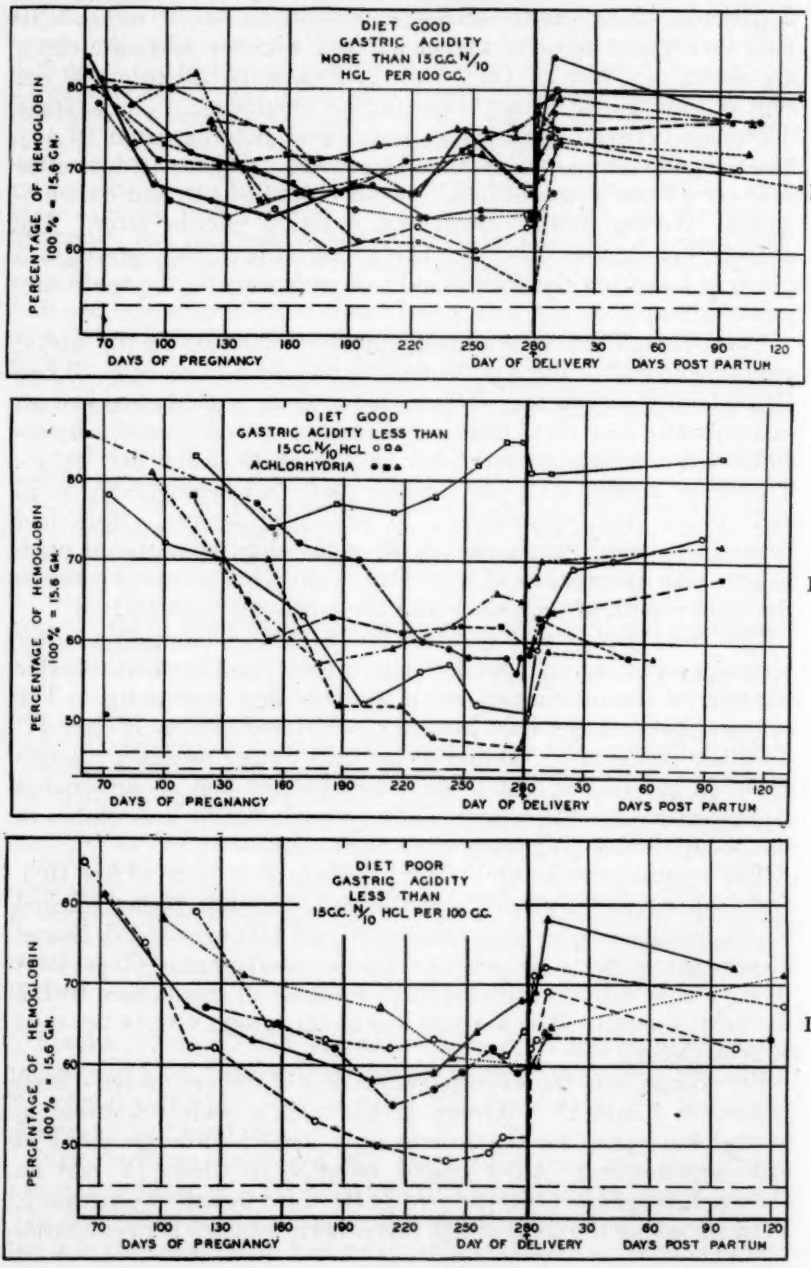
The third group of 3 patients had a total achlorhydria (after histamin injection) and had diets which were considered comparable to those of the individuals comprising the first two groups. The curves representing their hemoglobin determinations (Chart II) show low points of 58, 56 and 47 per cent during pregnancy, levels of 64, 63 and 59 per cent 10 days post-partum and no subsequent improvement 3 months later. The average loss of hemoglobin in this group during pregnancy was 18 per cent.

The 5 patients in Group IV had less than 15 cc. of N/10 free HCl, and took distinctly unsatisfactory diets. The low points reached by the hemoglobin during pregnancy (Chart III) were 48, 55, 58 and 61 per cent, respectively, with a return to an average of 69 per cent 10 days after delivery without further change of significance within the next 3 weeks. The average loss in this group was 14 per cent of hemoglobin.

For comparison, the average curves of 3 of the groups have been plotted in Chart IV. (Group II has such a wide dispersion in hemoglobin values for the 3 cases as to make an average curve of little significance.) All 3 groups recorded in Chart IV had an average hemoglobin of 80 per cent in the third month of pregnancy. Until the end of the sixth month there was less than 5 per cent varia-

* Eggs, 2 daily; meat, twice daily; fruit, 2 to 3 times daily; 3 to 4 helpings of vegetables daily.

CHARTS I, II, III.—HEMOGLOBIN DETERMINATIONS OF 20 WOMEN DURING AND AFTER PREGNANCY.



tion between them. However, in the last trimester the group of 9 patients with good diets and more than 15 cc. N/10 free HCl showed a slight gain of hemoglobin, whereas both the group with achlorhydria and the group with poor diet continued to decline, the former to a slightly greater degree than the latter. Ten days post-

CHART IV.—ARITHMETIC AVERAGE HEMOGLOBIN CURVES OF 17 PREGNANT WOMEN GROUPED ACCORDING TO DIET TAKEN AND AMOUNT OF GASTRIC HYDROCHLORIC ACID.

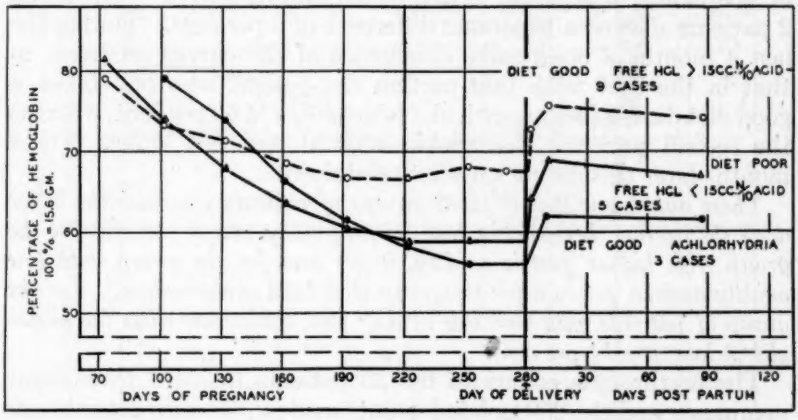
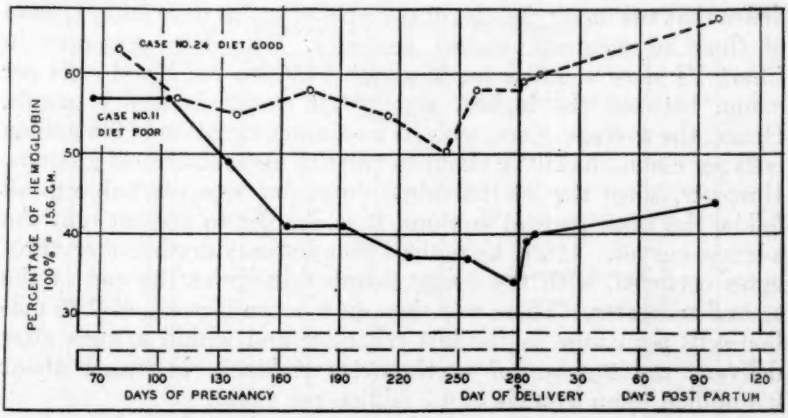


CHART V.—HEMOGLOBIN DETERMINATIONS OF 2 PREGNANT WOMEN DISTINCTLY ANEMIC AT THE ONSET OF PREGNANCY, 1 TAKING A POOR DIET, THE OTHER A GOOD DIET.



partum the hemoglobin of the first group averaged 76 per cent, of the group with poor diet 69 per cent, and of the group with achlorhydria 62 per cent. Three months later no significant changes had occurred, and the latter two groups continued to have on the average less than 70 per cent of hemoglobin.

Data for the 2 cases (11 and 24), which were distinctly anemic when first seen early in pregnancy, are shown separately in Chart V. Both patients had taken inadequate diets throughout their lives. Both had gastric acidity during pregnancy of less than 15 cc. N/10 free HCl. Patient 24, however, began at the onset of pregnancy to eat much meat, fruit and green vegetables, and continued to do so. Patient 11 continued with her previous very unsatisfactory diet throughout pregnancy and thereafter. During the first 5 months of pregnancy, 3 separate hemoglobin examinations of each of the 2 patients showed a maximum difference of 6 per cent. During the last 4 months a progressive divergence of the curves occurred, so that in the first week post-partum the patient who had taken a good diet during pregnancy had a hemoglobin of 60 per cent, whereas the second patient's hemoglobin was 20 per cent lower. Three months later this difference was maintained.

These data show that of the 3 groups of patients who took the better diets the average hemoglobin loss in pregnancy was 5 per cent for the group with higher gastric acidity, 9 per cent for the group with low acidity and 18 per cent for the group with total achlorhydria. For the group of patients with both low acidity and inadequate diets the hemoglobin loss was 14 per cent.

The erythrocyte counts of the 20 patients followed throughout pregnancy and the 200 isolated counts made upon different subjects in the various months of pregnancy (Chart VI) show no essential difference in the general distribution of the two groups or in their arithmetic average curves. This was considered presumptive evidence that the blood changes of the smaller group were fairly typical of those of pregnant women generally. The data presented in Chart VI show a difference of about 2 million red blood cells per c.mm. between the highest and lowest counts in any 1 month. Hence, the average curve, with its maximum variation of 0.8 million cells per c.mm., has little claim to validity upon statistical grounds. However, since the 20 individual curves of separate subjects all follow the same general contour, it is simpler to present only the average curves. It will be noticed that a steady decline of erythrocytes occurred, with the lowest counts usually at the end of the second trimester. There was then an average increase of 0.25 million cells per c.mm. in the last trimester and within a week after delivery the number of erythrocytes suddenly increased about 0.5 million to an average of 4.5 million per c.mm.

The results of 200 hemoglobin determinations throughout pregnancy and after delivery show (Chart VII) an average variation of 30 per cent between high and low values in any 1 month. The average curve is presented for comparison with the curves of Charts I and IV. It shows a progressive decline during the first 2 trimesters of pregnancy followed by a rather stationary course until delivery and then a sudden gain of 5 per cent. These curves are in essential agreement with those of Kühnel.[13]

CHART VI.—ERYTHROCYTE COUNTS ON 200 DIFFERENT WOMEN IN DIFFERENT MONTHS OF PREGNANCY AND IN THE PUERPERIUM (OPEN CIRCLES) AND 220 ERYTHROCYTE COUNTS ON 20 PATIENTS THROUGHOUT PREGNANCY AND AFTER (SOLID DOTS). THE ARITHMETIC AVERAGE CURVE OF THE OPEN CIRCLES IS SHOWN BY THE SOLID LINE; OF THE SOLID DOTS BY THE BROKEN LINE.

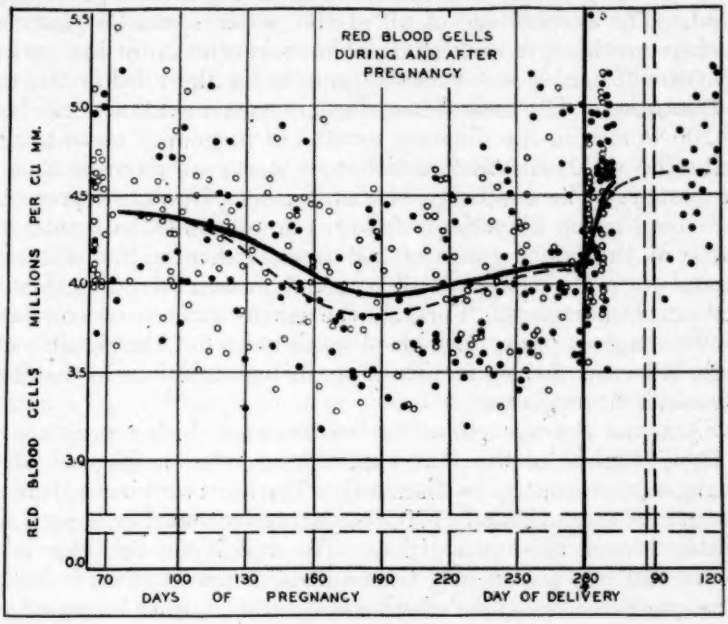
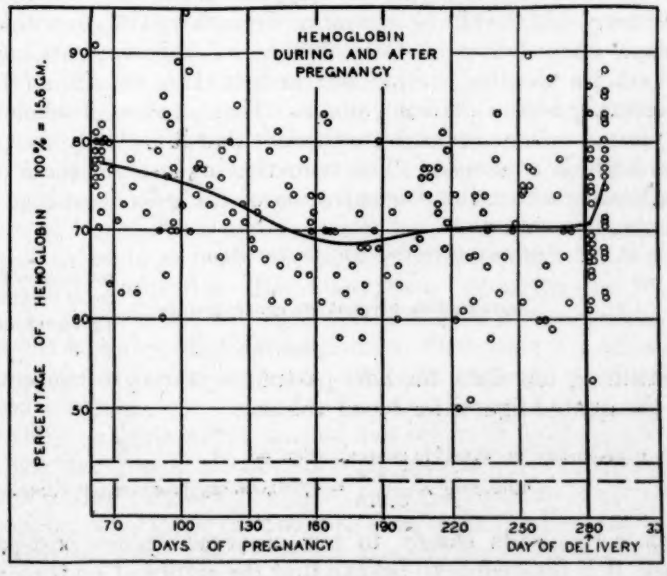


CHART VII.—HEMOGLOBIN DETERMINATIONS ON 200 WOMEN IN DIFFERENT MONTHS OF PREGNANCY AND IN THE PUERPERIUM.



Correlating the erythrocyte counts and hemoglobin determinations with the number of pregnancies and with the age of the patient, the averages for the patients in their third to fourteenth pregnancy were found to be the same as in those having their first or second child. The average age of all of the patients was 26 years; the average erythrocyte and hemoglobin concentration of the patients 26 years of age or over was the same as for those below 26 years.

Discussion. The data obtained from the examination of the blood of 200 women in the different months of pregnancy serve to illustrate the wide variations which may occur at any one time in pregnancy. The similarity of distribution of points representing the small group of patients followed from month to month, and those of the larger group of 200 cases, indicates that the small group was a fair sample of all pregnant women attending the Out-Patient Department. Further, the entire absence of correlation between age or parity and blood levels rules out the possible etiologic influence of these factors in producing variations in the degree of anemia in pregnancy.

Since the average curve for erythrocytes during pregnancy is roughly typical of the individual curves, the significance of the changes may properly be discussed. The most striking feature was the gain of approximately 500,000 mature red blood cells per c.mm. within 1 week after parturition. The rapidity of this gain is evidence that it is not entirely the result of increased blood formation. The question arises as to whether it is not merely an increased concentration due to a loss of plasma. The effect of dehydration in producing a concentration of the cellular elements of the blood is well known. Keith, Rowntree and Geraghty[14] have found that the average blood volume of women decreases 1100 cc. within 7 to 10 days after delivery. Only 300 cc. of this decrease may be ascribed to bleeding during parturition, the remaining 800 cc. representing loss of plasma volume. Their studies of whole blood and plasma volume corroborate the fact that it is chiefly the plasma volume which is reduced. This reduction in plasma without change in cells must affect the concentration of the cells according to the formula:

$$\text{Post-partum erythrocyte concentration} = \text{ante-partum erythrocyte concentration} \times \frac{\text{ante-partum blood volume}}{\text{post-partum blood volume}}$$

Substituting our data for ante-partum erythrocyte concentration and the quoted figures for blood volume:

$$\text{Post-partum erythrocyte concentration} = 4{,}050{,}000 \times \frac{5.876}{5.076} = 4{,}680{,}000 \text{ erythrocytes per c.mm.}$$

which corresponds closely to our observed values post-partum. Hence, it is reasonable to believe that the return of erythrocytes to

normal levels post-partum was due largely to a return of the blood volume to normal amounts and, conversely, that the decrease in erythrocyte concentration observed in the first six months of pregnancy was mainly due to the increasing blood volume. That the increase of plasma volume does occur in the first half of pregnancy rather than later is evidenced by the work of Bohnen and Borrmann.[15] However, carefully correlated studies of blood volume and cell concentration must be performed before this hypothesis can be accepted.

Two other theories may be mentioned at this point. The first, that a toxic hemolysin is produced by the fetus or placenta,[16,17,18] is unsound, since there is no evidence that such a factor exists or that there is increased hemolysis under the conditions of normal pregnancy. The second, that toxic inhibition of the bone marrow occurs, lacks, in the first place, evidence for the existence of a toxin; second, evidence of inhibition of the leukocytes[19] such as is found in other types of toxic action on the bone marrow; and third, evidence that the hemoglobin returns to normal during the 3 months after delivery when the toxic factor should no longer be present.

Assuming that the changes occurring in hemoglobin and erythrocyte concentration during the first half of pregnancy and in the week post-partum are due to plasma volume changes, it is to be observed that the actual differences in hemoglobin concentration in different patients manifest themselves during the *last* half of pregnancy. This is the period during which the fetus is laying down its chief supply of blood-building materials,[20,21,22] which must of necessity be derived from the maternal organism. In this respect it is significant that the babies of the 22 women studied all had normal erythrocyte counts and hemoglobin values. A reasonable hypothesis would thus be that the cause of anemia beyond a degree attributed to alteration of plasma volume in the mother lies in an inadequate supply of these building materials to meet both the fetal and the maternal demand.

In the absence of complications such as hemorrhage the factors that may reasonably be considered to influence the maternal supply of hemoglobin building materials are two: (1) The amount of such material taken in as food; (2) the absorption of such material after ingestion, or utilization after absorption. Studying the 20 cases from the point of view of food intake and of gastric acidity (as a measure of gastro-intestinal function[23]), there were 9 patients with both of these factors normal. In these patients no significant anemia occurred.

Of the 3 patients with a normal diet but with total achlorhydria, on the other hand, all developed a moderately severe grade of anemia during pregnancy, and 10 days post-partum their average hemoglobin was 62 per cent as compared to 76 per cent for Group I mentioned above. The 5 patients who had poor diets and moderate reduction in gastric acidity showed the development of moderate

anemia with an average 10-day post-partum hemoglobin of 69 per cent. Two patients with moderate reduction in gastric acidity, and diets as satisfactory as commonly taken, showed less anemia than those individuals with poor diets, and, furthermore, during the first 3 months post-partum, when their gastric juice had returned to normal, they had a progressive gain in hemoglobin. A third patient who had an unusually satisfactory diet, failed to develop any appreciable anemia.

The existence of anemia prior to the beginning of pregnancy apparently need not condition anemia of greater degree during pregnancy. This is illustrated by the course of the 2 patients mentioned above, both of whom had a moderate anemia associated with inadequate diets before they became pregnant. The one who continued to eat poorly became severely anemic during pregnancy while the other, who ate well from the beginning of pregnancy, actually gained hemoglobin during the course of her pregnancy.

The anemia of these pregnant women thus differed in no distinctive way from anemia associated with chronic blood loss, poor diet or gastric anacidity. In these patients the demands of the fetus for hemoglobin-building materials represented blood loss just as definitely as would menorrhagia, and pregnancy depressed the gastric acidity even in those patients who later showed normal values. The type of dietary deficiency (low intake of protein, iron and perhaps other metals) encountered in some of these patients with anemia is the same as that noted by Mettier and Minot,[23] and others in patients with hypochromic anemia, and the rôle of gastric anacidity in the production of this type of anemia has been repeatedly emphasized.[8,23,24,25,26,27] In short, then, in pregnancy the combination of the loss of blood-building materials to the baby, the lowering of the gastric acidity and, in many cases, the alteration of the diet of the patient, produces anemia by the same mechanisms that produce similar types of anemia in the nonpregnant individual.

Conclusions. 1. Anemia in pregnancy (reduction in the *total* hemoglobin content of the mother's blood) occurs during the last trimester of pregnancy when the fetus draws upon the maternal organism for blood-building, muscle-building and storage materials and is found only in those patients who have had for a considerable time a defective diet or dietary deficiencies conditioned by gastric anacidity or related gastro-intestinal disturbances.

2. The "physiologic" reduction of erythrocytes during pregnancy is probably due to hydremia and is not a true anemia.

3. These observations suggest the importance of an optimal diet and one especially rich in proteins and iron-containing foods for the prevention of anemia in pregnancy.

It is a pleasure to acknowledge our indebtedness to the visiting surgeons and house staff of the Obstetrical Service of the Boston City Hospital, through whose coöperation this study was made possible.

The technical work on the blood was chiefly performed by Miss Margaret Evans and Miss Elizabeth King.

BIBLIOGRAPHY.

1. Bland, P. B., Goldstein, L., and First, A.: Secondary Anemia in Pregnancy and in Puerperium, Am. J. Med. Sci., 1930, **179**, 48.

2. Pepper, O. H. P.: A Review of Our Knowledge of the Anemias of Pregnancy, Med. Clin. North America, 1929, **12**, 925.

3. Bland, P. B., Goldstein, L., and First, A.: The "Physiological" Anemia of Pregnancy, Surg., Gynec. and Obst., 1930, **40**, 954.

4. Nalle, B. C.: Anemia of Pregnancy, South. Med. J., 1930, **23**, 490.

5. Moore, J. H.: Anemia in Pregnancy, Am. J. Obst. and Gynec., 1930, **20**, 254.

6. Jerlov, E.: Hemoglobin Deficiency in Pregnancy and a Suggestion for the Prophylaxis of Anemia, Acta Obstet. et Gynecol., 1929, **8**, 356.

7. Galloway, C. E.: Anemia of Pregnancy, J. Am. Med. Assn., 1929, **93**, 1695.

8. Strauss, M. B.: Chlorotic Anemia of Pregnancy, Am. J. Med. Sci., 1930, **180**, 818.

9. Yang, C. S., and Keefer, C. S.: The Anemias of Pregnancy, Nat. Med. J. China, 1930, **16**, 159.

10. Wills, L., and Mehta, M. M.: Studies in "Pernicious Anemia" of Pregnancy, Ind. J. Med. Res., 1930, **17**, 777. Wills, L., and Talpade, S. K.: Ibid., 1930, **18**, 283. Wills, L.: Treatment of "Pernicious Anemia of Pregnancy" and "Tropical Anemia" with Special Reference to Yeast Extract as a Curative Agent, Brit. Med. J., 1931, i, 1059.

11. Castle, W. B., Heath, C. W., and Strauss, M. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia, IV, Am. J. Med. Sci., 1931, **182**, 741.

12. Strauss, M. B., and Castle, W. B.: Studies of Anemia in Pregnancy. I. Gastric Secretion in Pregnancy and the Puerperium, Am. J. Med. Sci. (preceding article).

13. Kühnel, P.: Untersuchungen über die physiologische Schwangerschaftsanämie, Ztschr. f. Geburtsh. u. Gynäk., 1926, **90**, 511.

14. Keith, N. M., Rowntree, L. G., and Geraghty, J. T.: A Method for the Determination of Plasma and Blood Volumes, Arch. Int. Med., 1915, **16**, 547.

15. Bohnen, P., and Borrmann, K.: Untersuchungen über die Vermehrung der Blutmenge in der Schwangerschaft, Arch. f. Gynäk., 1925, **126**, 144.

16. Hofbauer, J.: Für die placentare Theorie der Eklampsie-ätiologie, Zentralbl. f. Gynäk., 1908, **32**, 1469; Die Ätiologie der Eklampsie, Ibid., 1918, **42**, 745.

17. Allan, W.: Hemolytic Anemia in Pregnancy, Surg., Gynec. and Obst., 1928, **47**, 669.

18. Suwa, Y.: Hematologic Investigation of Anemia in Pregnancy, Japanese J. Obst. and Gynec., 1930, **13**, 583.

19. Unpublished data.

20. Hoogounenq, L.: Recherches sur la statique des éléments numeraux et particulièrement du fer chez le foetus humain, Compt. rend. Acad. d. sc., 1899, **128**, 1054.

21. Zeidberg, L. D.: A Quantitative Determination of the Changes in Hemoglobin Concentration, Volume of Red Cells and Basophilia in the Blood of Rabbit Fetuses at Various Stages During the Last Third of Pregnancy, Am. J. Physiol., 1929, **90**, 172.

22. Smythe, C. V., and Miller, R. C.: The Iron Content of the Albino Rat at Different Stages of the Life Cycle, J. Nutrition, 1929, **1**, 209.

23. Mettier, S. R., and Minot, G. R.: The Effect of Iron on Blood Formation as Influenced by Changing the Acidity of the Gastroduodenal Contents in Certain Cases of Anemia, Am. J. Med. Sci., 1931, **181**, 25.

24. Faber, K.: Achylia Gastrica mit Anämie, Med. Klin., 1909, **5**, 1310; Anämische Zustände bei der Chronischen Achylia Gastrica, Berl. klin. Wchnschr., 1913, **1**, 958.

25. Witts, L. J.: Simple Achlorhydric Anaemia, Guy's Hosp. Repts., 1930, **80**, 253.

26. Waugh, T. R.: Hypochromic Anemia With Achlorhydria, Arch. Int. Med., 1930, **47**, 71.

27. Davies, D. T.: Studies on Achlorhydria and Anaemia, Quart. J. Med., 1931, **24**, 447.

THE OCCURRENCE OF SICKLEMIA IN THE WHITE RACE.

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It is generally believed that the presence of sickle cells in the blood occurs only in the negro race or in those with an admixture of negro blood. This belief is based on reports of numerous examinations for sickle cells in the bloods of both colored and white persons either normal or diseased. The incidence of the sickling trait among unselected negroes seems to be about 7 per cent, as determined by averaging the various figures by writers on the subject.

Sickling of the red blood cells or sicklemia (a term used to designate such a condition of the blood) is not in itself a manifestation of disease, since it can be found in perfectly healthy individuals who never have had anemia. It is a constitutional abnormality of the erythrocytes, probably traceable to a defect in their formation in the bone-marrow. The trait, which is hereditary and transmitted as a dominant character, according to the Mendelian law, is manifested by the transformation of normal round red cells into crescentic or sickle-like structures with pointed or filamentous ends. This transformation is best observed in a sealed wet preparation, wherein the process progressively increases in degree with the passage of time, until a maximum for a particular case has been reached. After the lapse of a certain period of time, varying from several days to 2 weeks, the distorted cells in the wet preparations usually return to their original round appearance. At any time during the period of sickling the affected cells may revert to their normal shape if the cover slip be removed from the wet preparation. When the process of sickling is incomplete, the cells appear shaped like oat or caraway seeds. Stained blood smears may show no characteristic sickling, or may show it in slight and often incomplete degree; rarely do they show the sickling to the degree seen in corresponding sealed wet preparations.

In a small proportion of cases with sicklemia the affected red blood cells are attacked and destroyed by the cells of the reticuloendothelial system, especially by those of the spleen; and a hemolytic type of anemia results. The term "sickle-cell anemia" is applied to this form of anemia. Although Herrick[1] in 1910 was the first to report the presence of sickle cells in a case of severe anemia, it is to Sydenstricker[2,3] and to Huck[4] that we owe most of our knowl-

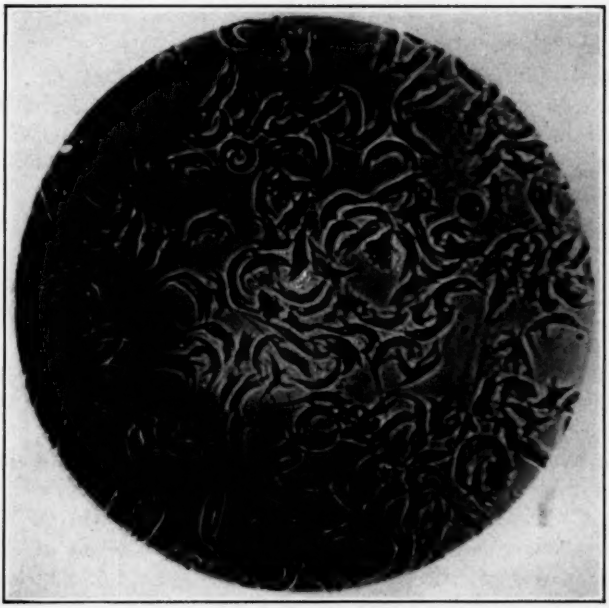

FIG. 1.—Patient's blood in a sealed wet preparation after 24 hours. (No. 138193.)

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edge of sickle-cell anemia as a clinical entity. Comprehensive reviews of the subject have been published by Graham and McCarty[5] and by Steinberg.[6]

The marked resemblance of sickle-cell anemia to congenital hemolytic icterus has been noted by a majority of writers on the subject. Among the important differences, aside from the sickling of the red blood cells, are the existence of macrocytosis in the stained smears and an increased resistance of the erythrocytes to hypotonic salt solution in sickle-cell anemia, whereas in congenital hemolytic icterus there is microcytosis and a decreased resistance. These differences proved to be of utmost value in the recognition of the case of sickle-cell anemia reported in this paper.

From the ethnologic view-point there is great interest in the question as to whether sickle cells ever occur in white persons in whom there is no suspicion of admixture of negro blood. In the literature there is much confusion on this point, which is chiefly one to mistaking other deformities of the red blood cells for sickling or to a strong suspicion of admixture of negro blood in cases with true sickling.

Analysis of the literature with these possibilities in mind has resulted in the elimination of most of the cases from the category of sickle-cell anemia in a white person.

The first report of sickle-cell anemia in a white person is that of Castana[7] in 1925. In eliminating this case there are several points to be considered. In the first place, there are no illustrations. Second, there is no mention of the behavior of the patient's red cells in sealed wet preparations, an essential test in determining sickling. Third, and most important, is the fact that Castana's description of the semilunar or sickle-like gigantocytes and his references to these cells by other authors definitely identify them as "corps en demi-lune" of the French. Such cells represent degenerative erythrocytes and not true sickle cells. More recently they have been described by Schilling[8] and by Lambin and Leto.[9]

In 1926 a second case of sickle-cell anemia in a white person was reported by Archibald.[10] This was a typical case of sickle-cell anemia, illustrated by convincing photographs, in an Arab boy, aged 2 years, a native of the Sudan, Africa. The parents were both Arabs, and their blood showed no evidence of sickling. Nothing is stated of the possible presence of negro blood in the family tree, nor is any mention made regarding the appearance of the features of the patient or of his parents. Since the residence of the patient is in a region where the inhabitants are predominantly negro and where interbreeding is notoriously common, the probability of an admixture of negro blood in this case is very strong. For this reason this case cannot be regarded strictly as one of sickle-cell anemia in a white person who is free of the suspicion of an admixture of negro blood.

The third case, reported by Stewart,[11] was in an apparently white child, aged 6 years, with the facial characteristics of a negro—features of an octaroon, kinky hair, thick lips, and a flattened nose. The father was a healthy white man with no sickling in his blood and without any negro characters. The mother, who showed sickle cells in her blood, although considered a white person by her neighbors, had a dark skin and the features of a Cuban, and was of Cuban descent. It is well known that Cuba is a violent melting pot, with the negro the predominant type. Moreover, the family lived in a district bordering on the colored section. For these reasons this case also cannot be regarded strictly as within the category of sickle-cell anemia in a white person.

In 1927 Lawrence[12] reported elliptical and sickle-shaped erythrocytes in the blood of 6 white patients, and believed he was dealing with the sickle-cell trait. The photomicrographs, however, showed not the morphologic characteristics of true sickle cells, but a peculiar anomaly of the erythrocytes, wherein the latter have a constant elliptical form. In a later paper[13] Lawrence included the above cases as examples of the presence in the blood of elliptical erythrocytes and not of sickle cells.

In 1929 Cooley and Lee[14] reported a case of sickle-cell anemia in a white child of Greek descent. The description of the case and the photographs of the blood are convincing. This case we regard as the first one of sickle-cell anemia in a white person, in whom no reasonable suspicion can be raised of an admixture of negro blood.

In 1931 Sights and Simon[15] described a case of erythrocytic sickling with anemia in a white native American of Scotch-Irish parentage. The absence of a racial and geographical study of other members of the patient's family to exclude the possible admixture of negro blood decreases considerably the value of this case from an ethnologic viewpoint.

The following case is considered the third one of sickle-cell anemia in a white person where no evidence of admixture of negro blood can be discovered.

Case Report. M. Y. (No. 138193), a boy, aged 9 years, was admitted to the Jewish Hospital on April 9, 1931, on the service of Dr. B. Kramer. His chief complaint was intermittent attacks of abdominal pain for the past 5 years.

Family History. The father, who died 5 years ago, was born in the town of Reggio, Calabria, which is in southern Italy, where his family lived for generations and where negroes are unknown. A brother of his, whose blood shows no sickle cells, is certain that his parents and grandparents had no negro features. The mother of the patient, whose blood shows sickle cells and who as a child was anemic and in poor health, was born in the United States, where she has lived her entire life. She has a muddy complexion, but she has no features suggestive of the negro. She has 2 children, of whom 1 is the patient. The other child is a girl, aged 12 years, who has no feature suggestive of the negro and has sickle cells in her blood. The mother has 3 sisters and several brothers, none of whom shows anything suggestive of

TABLE 1.—BLOOD STUDIES IN THE CASE OF SICKLE-CELL ANEMIA IN A WHITE CHILD.

Date. 1931.	Hemoglobin per cent (Dare).	Erythrocytes millions per c.mm.	Color index.	Platelets thousands per c.mm.	Leukocytes thousands per c.mm.	Differential study.					Red cell studies.						Fragility tests with washed cells.		
						Poly. neut. per cent.	Poly. eosin. per cent.	Poly. baso. per cent.	Lymphocytes per cent.	Monocytes per cent.	Normoblasts per 100 W. B. C.	Reticulocytes per cent.	Macrocytosis.	Microcytosis.	Poikilocytosis and polychromasia.	Stippling	Beginning hemolysis.	Complete hemolysis.	Normal control using washed cells.
4/10	52	4.7	0.5	160	5.8	64.5	1	...	30	4.5	0	6	Mod.	Slight	Marked	+	0.40	0.20	0.46 to 0.30
(*a*) 4/20	50	4.9	0.5	...	12.4	60	2	...	34	4	0								
(*c*) 4/24	50	4.5	0.5	180	11.2	54	5	1	38	2	0.5	11	Mod.	Slight	Marked	+	0.42	0.22	0.44 to 0.32
(*d*) 4/24	51	4.6	0.5	280	32.0	43	4	1.5	47.5	4	0.5	10	Mod.	Slight	Marked	+	0.40	0.22	0.44 to 0.32
(*a*) 4/28	50	4.7	0.5																
(*b*) 5/17	40	3.9	0.5	...	9.0	57	..	...	43	...	0								
6/11	54	3.6	0.7	220	10.3	61	3	1	31	4	0.5	7	Marked	Slight	Marked	+			
9/26	60	5.2	0.5	150	9.1	63	4	0.5	29	3.5	0	10	Mod.	Slight	Marked	+			

REMARKS.—No sickle cells found in any of the smears; *a*, after an attack of abdominal pain; *b*, after a particularly severe attack of abdominal pain with cyanosis; *c*, before subcutaneous administration of 7 minims of adrenalin (1 to 1000); *d*, 15 minutes after administration of adrenalin.

the colored race. One of her sisters shows the sickling trait to a moderate degree.

The mother's parents and her forbears for generations were born and lived in Casabona, a town in Calabria, Italy. Here there has always been a strict social custom against intermarriage with other races. Negroes are unknown in this region; and in this connection it is interesting to note that the grandmother of the patient never saw a negro until she came to the United States at the age of about 25. The grandmother, who also shows sickle cells in her blood, was married in her native town, but gave birth to the patient's mother in the United States. She recalls her parents and grandparents on the paternal and maternal sides very well, and declares that they were all white in color, being even fairer in skin than the average Italian, and that they showed none of the facial characteristics of the negro race. By her appearance she certainly bears out this statement. Her husband, the grandfather of the patient, died several years ago of an unknown illness (see pedigree chart).

Past History. Negative.

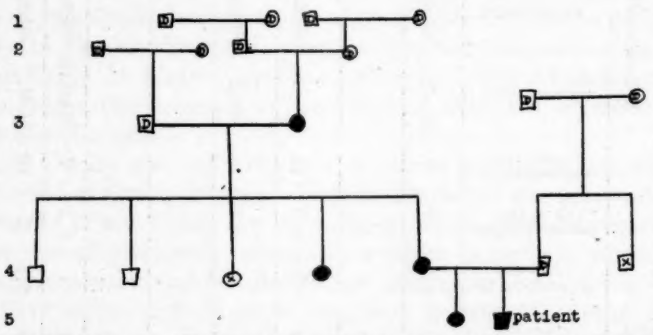

CHART I.—Family tree of patient, of which five generations can be recalled by its oldest living member and of which three generations show the sickling trait. Squares indicates males; circles, females. Black symbols indicate those with the sickling trait; symbols with cross inside represent negative examinations of blood for sickling; clear symbols indicate no examination of blood for sickling; symbols containing the letter *D* indicate dead persons. Numbers represent the generations.

Present Illness. Five years ago patient began to have attacks of severe abdominal pain, especially in the left upper quadrant, associated with inability to move the bowels but with no nausea or vomiting. The pain would persist for about 2 days, and then after a bowel movement it would disappear. These attacks recurred at intervals of 1 to 2 months at first, but later they increased in frequency, coming at intervals of 1 to 2 weeks. In the more recent attacks the pain was accompanied by fever. For the past year, weakness and profuse sweats have been noted.

Physical Examination. The patient showed no evidence of any negroid feature. There was a slight suggestion of a Mongoloid conformation of the eyes. The skin was a muddy yellowish color, and the mucous membranes were pale. The tonsils were small, buried, and apparently diseased. There was slight enlargement of the submaxillary and posterior cervical lymph nodes on each side; the other superficial lymph nodes were palpable but very small. There was a systolic blowing murmur over the precordium, transmitted to the left axilla. The blood pressure was 102/60. Abdominal examination revealed an enlarged spleen, reaching three fingers' breadth below the costal margin in the left nipple line. The liver edge was felt one

finger's breadth below the costal margin in the right nipple line. The extremities showed no ulcers or scars.

Laboratory Data. The blood Wassermann and Kahn reactions were negative. The uric acid was 4.2 mg., calcium 9.6 mg., phosphorus 4.8 mg., and cholesterol 184 mg., per 100 cc. of blood. The icterus index was 12. The van den Bergh test showed a positive direct delayed reaction and an indirect reaction of one unit. The urine was normal. Several urobilinogen and urobilin determinations ranged from 1200 to 2800 dilution units in 1000 cc. of urine and from 23,000 to 52,000 dilution units in the stools. The fragility tests and hematologic studies are reproduced in the accompanying table, and are later commented upon. Roentgenograms of the bones of the skull and of the extremities were negative.

Course. After 10 days in the hospital, the patient had an attack of severe upper abdominal pain, which was diffuse but worse in the left upper quadrant. At the same time he complained of severe headache and of pain in the joints of the right wrist and right knee. There were no objective arthritic signs. The scleræ which were previously clear now showed a slight icteric tinge. Four days after this attack, an adrenalin test was done, injecting 7 minims subcutaneously, a much larger dose than is ordinarily given. Within 1 minute the patient complained of epigastric pain, and had severe headache. On abdominal examination, the spleen was found to have receded from three fingers' breadth below the costal margin to such an extent that it was barely palpable beneath the costal margin. After 24 hours the spleen had returned to its original size.

During the following 4 weeks, the patient had about seven attacks of severe abdominal pain accompanied by severe headache and joint pains. Vomiting occurred when the headache was at its height; but not when abdominal pain alone was present. On three occasions a marked cyanotic spell occurred concomitantly with an attack, and it was necessary to use oxygen. On one such occasion a fatal termination seemed imminent. During the cyanotic attacks, his blood pressure was 132/80. Once the patient had a severe pain of stabbing character in the left side of his chest, aggravated by deep breathing. This was attributed to a splenic infarction. The temperature throughout ranged between 99° and 100.5° F, except for 2 days after one of the attacks of abdominal pain when it rose to 103°. The spleen remained unchanged in size during all the attacks.

The family of the patient refused to give permission for a splenectomy, and he was discharged May 26, 1931. Since his return home he has had frequent attacks of excruciating abdominal pain, usually in the left upper quadrant, but sometimes also in the right upper quadrant, accompanied by headache and joint pains, but with no cyanosis.

Hematologic Examination. The appended table shows the result of the various hematologic examinations. The important features to be noted are the low hemoglobin value with a relatively high erythrocyte count, giving a low color index, the mild degree of leukocytosis, the presence of normoblasts, reticulocytosis, macrocytosis, and the increased resistance of the red cells to hypotonic salt solution. It is worthy of note that no sickle cells were seen at any time in the stained smears, although there was a marked degree of poikilocytosis. It is also of interest to mention that, after one particularly severe attack of abdominal pain with headache and cyanosis, there was a significant increase in the degree of anemia. The urine was not tested for hemoglobin at this time, but the blood showed no gross evidence of hemolysis. The subcutaneous injection of adrenalin caused a prompt and marked contraction of the spleen, and produced a great increase in the number of leukocytes.

Sickling Phenomena. Wet preparations were made by placing a drop of blood on a very thin cover slip, inverting the latter on a glass slide, and

sealing the edges of the cover slip with vaseline. On immediate examination the preparations were entirely negative. After about 2 hours a few erythrocytes began to assume elongated, pointed forms, resembling oat or caraway seeds. In 24 hours, almost all of the red cells were transformed into typical sickle cells, as shown in the photomicrograph. On removing the cover slip the sickle cells immediately resumed their original round shape. If undisturbed the sickle cells kept their appearance for several days, and then began to become round again. In 7 to 10 days all the cells had returned to their original shape, and underwent no further changes except those of deterioration. It was also noted that occasionally a sealed wet preparation showed no sickling at all, although it was taken with the same technique and at the same time as positive preparations. Red cells washed four times with physiologic salt solution were likewise tested, and it was found that sickling took place to the same degree as in unwashed blood. Numerous attempts in this case to show the sickle cells on stained slides resulted in complete failure.

Because of the hereditary character of the sickling trait the blood of various members of the family of the patient were examined. The mother's blood showed a slight degree of sickling, about 3 to 5 per cent of the cells sickling in certain parts of the wet preparations. Her blood count was normal, the blood smears showed no abnormal red cells; the reticulocytes were less than 1 per cent; and the icterus index and the van den Bergh reaction were normal. The patient's sister, aged 12 years, had 1 per cent of sickle cells in her blood; her blood count, however, was normal, and stained smears showed no abnormal red cells. Her icterus index was 9; the van den Bergh reaction, direct, was negative and indirect, 1 unit; and the reticulocytes were less than 1 per cent. One of the maternal aunts of the patient showed from 10 to 20 per cent sickle cells in her blood. Two other maternal aunts and a paternal uncle had no sickle cells. Blood from the maternal uncles could not be obtained. The blood of the patient's maternal grandmother was found to have a few sickle cells, less than 0.5 per cent.

Comment. Thus the sickling trait has been definitely found in three generations of the above family; and in at least five generations it is known that the members have been of the white race. Nevertheless, the possibility cannot be absolutely ruled out that in a previous remote generation there might have been a negro ancestor with sickle cells in the blood and that the sickling trait, known to be transmitted as a dominant Mendelian character, might have been handed down thereby to white descendants with no external trace of any of the negro features. This possibility must receive serious consideration, for the weight of evidence at the present time seems to indicate the negro origin of sickling. That other races might be subject to the sickling trait has been suggested by Moore,[16] who found a high incidence of bone changes, similar to those that occur in some cases of sickle-cell anemia, in the skulls of the ancient Mayan Indians. Cooley and Lee[14] suggested that the sickling trait be looked for in those of the Mediterranean races presenting the picture of an atypical hemolytic icterus. Previously these authors[17] had described a peculiar form of atypical hemolytic icterus with bone changes in 7 children, 5 of whom were of Mediterranean racial origin. The entire subject is thus of unusual ethnologic interest.

Recognition of sickle-cell anemia in white persons may be facili-

tated if its resemblance to congenital hemolytic icterus is borne in mind. All cases of atypical hemolytic icterus, such as those with an absence of increased fragility of the erythrocytes or those with a macrocytosis instead of a microcytosis, deserve an examination of the blood for sickle cells. Since stained smears may fail to show such cells, it is necessary to make several sealed wet preparations, and to watch these for at least 24 hours before deciding on the presence or absence of sickling.

It is to be expected that in the future more cases of sickle-cell anemia in white persons will be discovered. The reasons for this statement are as follows: First, since attention has been called to the occurrence of the sickling trait in the white race, more frequent examinations of the blood for sickle cells will be made, especially in those patients presenting the syndrome of an atypical hemolytic icterus. Thus, more cases of the type described in this paper may be discovered. Second, since it is known that the sickling trait is a dominant character in its hereditary transmission and since interbreeding between the colored and the white races is more or less constantly taking place in many regions, including this country, we may in future generations expect the presence of this peculiar blood trait in an increasing number of apparently white descendants. Because of the tendency to deny such descent by those who are free of all negro features, no history will be obtained of such racial origin in affected individuals, thereby increasing the number of apparently pure white cases of sickle-cell anemia.

Summary. 1. A review of the literature of sickle-cell anemia in the white race reveals only one previous case where no evidence of a possible admixture of negro blood can be discovered. A second case is cited where the data are incomplete for such a conclusion.

2. A third case is here reported in a family where three generations show the sickling trait and at least five generations are known to be of the white race from a region where negroes are practically unknown.

3. The ethnologic and clinical feature of the subject are discussed.

4. Reasons are given for expecting an increase in the number of cases of sickle-cell anemia in the white race.

BIBLIOGRAPHY.

1. Herrick, J. B.: Arch. Int. Med., 1910, **6**, 517.
2. Sydenstricker, V. P.: South. Med. J., 1924, **17**, 177; J. Am. Med. Assn., 1924, **83**, 12; Med. Clin. No. Am., 1929, **12**, 1451.
3. Sydenstricker, V. P., Mulherin, W. A., and Houseal, R. W.: Am. J. Dis. Child., 1923, **26**, 132.
4. Huck, J. A.: Bull. Johns Hopkins Hosp., 1923, **34**, 335.
5. Graham, G. S., and McCarty, S. H.: South. Med. J., 1930, **23**, 598.
6. Steinberg, B.: Arch. Path., 1930, **9**, 876.
7. Castana, V.: La Pediatria, 1925, **33**, 431.
8. Schilling, V.: The Blood Picture—translated by Gradwohl, The C. V. Mosby Company, St. Louis, 1929, page 101; also plate I, Fig. 43, and plate III, Figs. 6 and 8.

9. Lambin, P., and Leto, A.: Rev. belge d. sci. méd., 1930, **2**, 246.
10. Archibald, R. G.: Trans. Roy. Soc. Trop. Med. and Hyg., 1926, **19**, 389.
11. Stewart, W. B.: Am. J. Dis. Child., 1927, **34**, 72.
12. Lawrence, J. S.: J. Clin. Invest., 1927, **5**, 31.
13. Lawrence, J. S.: Am J. Med. Sci., 1931, **181**, 240.
14. Cooley, T. B., and Lee, Pearl: Am. J. Dis. Child., 1929, **38**, 103.
15. Sight, W. P., and Simon, S. D.: J. Med., 1931, **12**, 177.
16. Moore, S.: J. Missouri Med. Assn., 1929, **26**, 561.
17. Cooley, T. B., Witwer, E. R., and Lee, P.: Am. J. Dis. Child., 1927, **34**, 347.

THE BASAL METABOLISM IN PERNICIOUS ANEMIA AND SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD.

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This investigation is part of an attempt to ascertain more about the nature of subacute combined degeneration of the cord and its relation to pernicious anemia by a study of systems other than that of the blood, nervous system and alimentary tract.

The observation, first pointed out to me by Dr. Wyman Richardson, that a low basal metabolic rate not infrequently exists in pernicious anemia, seemed of especial importance, since, from the various records in the literature of the basal metabolic rate in this disease, one was led to believe that the rate was more often either elevated or within normal limits than decreased. Therefore, during the course of an investigation concerning the effects of liver therapy in a large series of cases of pernicious anemia with and without subacute combined degeneration, opportunity was taken of noting the basal metabolic rate in a considerable number of cases. In addition, metabolic readings previously recorded in the Metabolism Laboratory of the Massachusetts General Hospital on patients with these diseases were incorporated into this series. Thus, estimations of the B.M.R. were obtained in 130 cases of pernicious anemia, and grouped according to whether or not subacute combined degeneration of the spinal cord was present. Comparative analyses of the metabolic rates in these two groups, and a discussion of the possible significance of the difference observed, together with a short review of the literature, form the subject of this paper.

In this series of 130 cases, the basal metabolic rates of 36 patients, of whom 12 had spinal cord involvement, were determined before liver treatment was instituted. However, since no significant alterations in the ultimate results were found on separating the basal

metabolic rates of the liver-treated cases from those of patients who were not so treated, it was considered that all the cases could be analyzed together.

In the diagnosis of subacute combined degeneration of the cord, the criteria followed were identical with those used elsewhere[1,2] and which may be reiterated here. This group includes only those cases of pernicious anemia which have shown definite signs of involvement of either the posterior or lateral columns of the spinal cord, or of both these columns, Incoördination and ataxia from loss of muscle and joint sensibility, and in addition loss of vibration sense, are the signs which have been regarded as evidence of involvement of the posterior columns. The "extensor" type of plantar reflex (Babinski's sign), with or without exaggeration of the deep reflexes, and patellar or ankle clonus, are the signs used to indicate degeneration of the pyramidal fibers of the lateral columns. Although it is realized that in pernicious anemia numbness and tingling of the extremities are probably indicative of involvement of the peripheral nerves or even possibly of the spinal cord, the presence of such symptoms alone has not been regarded as sufficient to warrant a diagnosis of subacute combined degeneration. Such cases, therefore, were included in the uncomplicated pernicious anemia group. However, in order to ascertain into which group the basal metabolic rate of these cases would tend to fall, they were further segregated from the general pernicious anemia group and plotted. It will be seen from Chart I that these cases of pernicious anemia with paresthesia alone and those without these symptoms are similarly distributed, contrasting markedly with those diagnosed as pernicious anemia with subacute combined degeneration. According to the above diagnostic criteria, this series of 130 cases consists of 65 instances of pernicious anemia with, and a similar number without, subacute combined degeneration.

All the determinations were carried out on the Benedict-Roth basal metabolism apparatus. When two or more readings were obtained on the same patient the lowest was always used, since by so doing the error entailed is least. In the few instances in which fever was present during the test, the reading was corrected according to the DuBois formula of 7.2 per cent reduction per 1° F. All cases presenting either thyrotoxicosis or myxedema were excluded from this series, the coexistence of the latter condition and pernicious anemia having already been reported from this clinic.[3]

From Table 1 it will be seen that of the 65 cases of pernicious anemia without spinal cord involvement, 41.5 per cent have a basal metabolic rate above +10 per cent and there is none below −9 per cent, whereas of the 65 cases of pernicious anemia with subacute combined degeneration only 3 per cent have a rate above +10 per cent and there are 43.1 per cent with a basal metabolism of −10 per cent or less.

TABLE 1.—DISTRIBUTION TABLE OF THE BASAL METABOLISM IN PERNICIOUS ANEMIA, WITH AND WITHOUT SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD.

Basal metabolic rate.	Pernicious anemia without spinal cord involvement (65 cases), per cent.	Pernicious anemia with spinal cord involvement (65 cases), per cent.
Above +20	18.5	0.0
+11 to +20	23.0	3.0
+1 to +10	40.0	18.5
0 to −9	18.5	35.4
−10 to −19	0.0	32.3
−20 and under	0.0	10.8

The tendency for elevated metabolic rates to be found in pernicious anemia and other forms of anemia has been pointed out by several investigators, *e.g.*, Magnus-Levy,[4] Rolly[5] and Meyer and Du Bois.[6] Boothby and Sandiford[7] in a group of 19 cases of pernicious and splenic anemia found that 15.9 per cent had a basal metabolism below −10 per cent and 21.1 per cent above +10 per cent. In a later publication,[8] bearing on 36 cases of pernicious and splenic anemia, only 6 per cent had rates below −10 per cent whereas in 41 per cent the basal metabolism was above +10 per cent. These figures are very similar to those obtained in the present series of cases of pernicious anemia without spinal cord involvement. Tompkins, Brittingham and Drinker,[9] in a series of 12 cases of pernicious anemia, pointed out that the recent more acute cases gave an elevated metabolic rate, whereas a diminished rate was the rule in the long-standing chronic cases. It would have been interesting to know whether or not neurologic involvement was a feature in these chronic cases with low metabolic rates. These investigators also made the important observation that in all cases the metabolic rate fell when the red blood cell level increased as a result of blood transfusion. Coincident with the fall in the metabolic rate and the increase in the numbers of red blood cells, there was a diminution in the pulse and respiration rates and a fall in temperature. The tendency to elevation of the basal metabolic rate in pernicious anemia and its diminution during remission has also been noted by other investigators.[10,11,12] Alt[12] made a study of 5 cases of pernicious anemia treated with liver extract, noting the basal metabolism at intervals throughout the remissions. He observed that the metabolic rate, normal at first, rose during the reticulocyte crisis, fell rapidly during the increase of red blood cells and finally returned to within normal limits. The diminution in basal metabolism during the formation of new red blood cells was accounted for, according to this writer, by the fact that when ingested protein is deposited as new tissue, its animo acids cease to exert a specific dynamic action on metabolism. Decrease in pulse and respiration rate, and in the temperature, and again in body weight were also considered as contributory causes. Richards and Strauss[11] pointed

out that in anemia, in addition to a tendency for the basal metabolic rate to be elevated, there is an increase of the cardiac output and of the percentage utilization of oxygen by the tissues. These two latter adjustments were considered the means by which the burden of the diminished oxygen capacity on the circulation is borne, and, together with the elevated basal metabolism, diminished coincident with the remission of the anemia. That there is a tendency for the basal metabolism to diminish coincident with amelioration of the anemia is confirmed by several instances in the present series of cases, in which metabolic rates were determined in the same case at different levels of the red blood cell count.

Since it is evident that the basal metabolism in any given case depends to a large extent on the red blood cell level, and since there is a tendency for cases of pernicious anemia with neurologic involvement to come under observation with a lesser degree of anemia than those without such involvement, it was considered possible that the marked disparity in the metabolism of these two groups may be accounted for by differences in the red blood cell counts. In order to ascertain to what extent this may have been the case, the metabolic readings in each group were plotted against their respective red cell counts (Chart I). Moreover, it was considered that this procedure would tend also to obviate any discrepancies which may arise due to the fact that almost all the red blood cell counts of the cases not treated with liver were less than 3 millions per c.mm., in contrast to those of the liver-treated patients, in whom there was a large proportion of red blood cell counts above this level.

From Chart I, it is evident that at any given red blood cell level, there is a distinct tendency for the basal metabolism in pernicious anemia with subacute combined degeneration to be substantially lower than in pernicious anemia without involvement of the central nervous system. It is evident, therefore, that the difference between the two groups is more than can be accounted for by differences in the red blood cell levels.

Furthermore, analyzed statistically,* it is found that the ratio of the difference between the mean basal metabolism of each group (20.2), to the probable error of the difference between the means (1.17) is 17. From this it may be concluded that the odds against the occurrence of such a difference as found between the two means is so great as to make it practically certain that the basal metabolism is lower in the group of cases with spinal cord involvement. It is of interest that Williams[13] has observed diminished basal metabolic rates in several cases of subacute combined degeneration of the cord.

The tendency for a low metabolic rate to be found in pernicious anemia with subacute combined degeneration may conceivably be explained on the basis of the neuromuscular disability and the

* Kindly carried out by Dr. I. M. Rabinowitz of Montreal General Hospital.

curtailing of general body activities, thereby slowing up oxidation processes. In order to ascertain to what extent this hypothesis may be true, the basal metabolic rates of the patients with subacute combined degeneration were further analyzed according to the degrees of disability. For this purpose the cases were separated into certain convenient, though arbitrary, groups, as follows: (1) those who were bedridden, (2) those who required crutches or aid in order to walk, (3) those who could get about with the help of a cane, (4) those in whom there was slight unsteadiness on walking, and (5) those who were able to walk "essentially" normally.

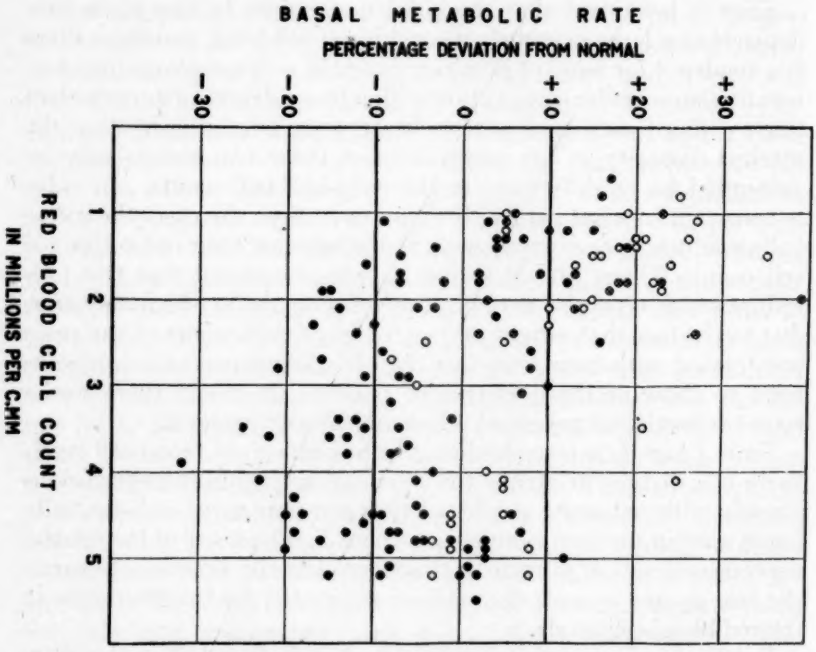

CHART I.—The relation of the basal metabolism to the red blood cell level in pernicious anemia, with and without subacute combined degeneration of the spinal cord.

○, Denotes pernicious anemia without paresthesiæ
⊕, Denotes pernicious anemia with paresthesiæ only
} . . . . . 73 basal metabolic readings on 65 patients.

●, Denotes pernicious anemia with subacute combined degeneration . . . . . 71 basal metabolic readings on 65 patients.

On comparing the basal metabolism of these five groups, it was found that there was no greater tendency for bedridden patients to have low basal metabolism than for those with only slight unsteadiness on walking, or for those with intermediate grades of disability. It is noteworthy, however, that in all the 11 cases in which liver treatment had brought about almost complete relief from neuromuscular disability, the basal metabolic rates were within normal

limits, and this in spite of the high level of red blood cell counts in this group (see Table 2). Unfortunately, no data are available concerning the basal metabolism in these 11 patients before liver treatment was commenced, or before their difficulty in walking had completely disappeared.

TABLE 2.—THE BASAL METABOLISM IN 65 CASES OF PERNICIOUS ANEMIA WITH SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD, GROUPED ACCORDING TO THE DEGREE OF DISABILITY.

Degree of disability.	No. of cases.	Average B.M.R., per cent.
Bedridden	18	−10.0
Crutches	8	− 6.4
Cane	12	− 9.0
Slight unsteadiness	16	− 9.1
None	11	− 2.3
Totals	65	− 7.9

On account of the tendency for the basal metabolism to become elevated when the red blood cell level is diminished, it must be realized that the average basal metabolic rates of each of the above groups are not strictly comparable. In order to obviate this discrepancy, all the basal metabolic rates determined in patients with red blood cell counts below 3.5 millions per c.mm. were discarded. The remaining 39 cases were compared and the results are given in Table 3. It may be seen that this process of elimination brought about a slightly lower average basal metabolic rate for each group, the diminution being greatest in the bedridden group, and negligible in individuals with no disability. Although the number of cases available for consideration is thus considerably reduced, giving the results, as a whole, perhaps somewhat less significance, elimination of the low red blood cell counts ensures, at least, that all the basal metabolic rates are comparable.

TABLE 3.—THE BASAL METABOLISM IN 39 CASES OF PERNICIOUS ANEMIA WITH SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD WITH RED BLOOD CELL COUNTS OF 3.5 MILLIONS PER C.MM. AND OVER, GROUPED ACCORDING TO THE DEGREE OF DISABILITY.

Degree of disability.	No. of cases.	Average B.M.R., per cent.
Bedridden	8	−14.8
Crutches	3	− 8.0
Cane	9	− 9.8
Slight unsteadiness	10	−11.2
None	9	− 2.4
Totals	39	− 9.3

From the above data, it seems that the finding of a marked difference between the average basal metabolic rates of the patients with and of those without neuromuscular disability is not incompatible with the hypothesis that disability is the factor responsible for the tendency for a diminished oxygen consumption in subacute combined degeneration. However, it is difficult to conceive why

the patients with but slight unsteadiness on walking should also tend to have a diminished basal metabolism. Moreover, if the hypothesis that disability may be the cause of this diminution were true, one would expect similar low readings in other crippling nervous disorders, such as tabes dorsalis, disseminated sclerosis, transverse myelitis, and the like. Although the data on this subject are comparatively scanty, it appears that in such conditions the oxygen consumption is usually within the normal limits. Of 20 cases of sclerosis of the central nervous system and tabes dorsalis, reported by Boothby and Sandiford,[7] 90 per cent had a basal metabolism between −10 per cent and +10 per cent, the remaining 10 per cent being between +11 per cent and +15 per cent. Grafe,[14] while studying the basal metabolism in such neurologic conditions as encephalitis lethargica, multiple sclerosis, traumatic transverse myelitis, etc., noted that the metabolism was within normal limits, regardless of whether the paralyses were of the spastic or of the flaccid type. It is of interest to note that this writer pointed out that in neurologic conditions, hypertonicity, spasm, and even tremor of the muscles do not tend to increase the basal oxygen consumption, and believed that muscles under these conditions are able to work more economically than in the case of voluntary contractions.

Although it is not unlikely that the tendency for a low basal metabolism to be a feature in subacute combined degeneration may be explained on the basis of neuromuscular disability, the evidence in support of such an hypothesis is not conclusive, and it is possible that some other factor may be responsible.

Several of the patients with diminished basal metabolism exhibited definite, though usually mild, hypothyroid symptoms, but in no case was true myxedema present. Such symptoms as dry skin, absence of perspiration, intolerance to cold and a poor memory were commonly noted. It is noteworthy that a low basal metabolic rate was not always accompanied by symptoms which occur with hypothyroidism.

Relief from such symptoms, and a return of the diminished basal metabolism to normal, were readily brought about by the administration of thyroid extract, the usually daily dose being 3 grains of Armour's preparation, but in no instance could improvement in the neurologic condition be attributed to this drug. The administration of liver, while resulting usually in marked neurologic benefit, did not appear to have any appreciable effect on the hypothyroid symptoms.

Summary. 1. The basal metabolic rates of 65 cases of pernicious anemia without, and of 65 cases with, subacute combined degeneration of the spinal cord have been studied.

2. In pernicious anemia without spinal cord degeneration, the basal metabolism tends to be either normal or elevated (41.5 per cent of the cases had a B.M.R. of over +10 per cent), but in per-

nicious anemia with subacute combined degeneration there is a distinct tendency for diminution to occur (43.1 per cent had a B.M.R. below −9 per cent).

3. The basal metabolism is influenced by the level of the red blood cells. In the cases with subacute combined degeneration the red blood cell counts were, on the whole, higher than in the group of patients with uncomplicated pernicious anemia. The data show, however, that the tendency for diminution of the B.M.R. to occur in patients with subacute combined degeneration of the cord exists at all levels of the red blood cells. Therefore the red blood cell level cannot be regarded as the responsible factor.

4. Consideration is given to the possibility that the diminished basal metabolism in cases with subacute combined degeneration may be the result of neuromuscular disability.

5. The symptomatology and the effects of thyroid administration in the cases with low basal metabolism are presented.

NOTE.—I am grateful to Dr. J. H. Means for permission to use the cases in the Medical Services and Outpatient Departments of the Massachusetts General Hospital, and for facilities extended in the Metabolism Laboratory. I am also indebted to Dr. J. Lerman and the Staff of the Metabolism Laboratory for their kind coöperation, and to Dr. G. R. Minot for his kindly help and criticism.

REFERENCES.

1. Ungley, C. C., and Suzman, M. M.: Brain, 1929, **52**, 271.
2. Suzman, M. M.: Trans. Am. Neurol. Assn., 1931. (In press.)
3. Means, J. H., Lerman, J., and Castle, W. B.: New Eng. J. Med., 1931, **204**, 243.
4. Magnus-Levy, A.: Ztschr. f. klin. Med., 1906, **60**, 179.
5. Rolly, F.: Deutsch. Arch. f. klin. Med., 1914, **114**, 605.
6. Meyer, A. L., and Du Bois, E. F.: Arch. Int. Med., 1916, **17**, 965.
7. Boothby, W. M., and Sandiford, I.: J. Biol. Chem., 1922, **54**, 783.
8. Boothby, W. M., and Sandiford, I.: Phys. Rev., 1924, **4**, 69.
9. Tompkins, E. H., Brittingham, H. H., and Drinker, C. K.: Arch. Int. Med., 1919, **23**, 441.
10. Grassheim, K.: Ztschr. f. klin. Med., 1929, **111**, 601.
11. Richards, D. W., and Strauss, M. L.: J. Clin. Invest., 1928, **5**, 161.
12. Alt, H. L.: Arch. Int. Med., 1929, **43**, 488.
13. Williams, J. P.: Personal Communication; also Bull. McGuire Clinic and St. Luke's Hospital, 1929, **1**, 133.
14. Grafe, E.: Deutsch. Arch. f. klin. Med., 1922, **139**, 155.

THE DIFFERENTIATION OF LYMPHATIC LEUKEMIA FROM AGRANULOCYTIC ANGINA.

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MANY cases of agranulocytic angina have been reported in the literature since this was given importance as a supposedly clinical entity by Schultz[1] in 1922 and by Kastlin[2] in this country in 1927.

That the condition had been reported previously to these papers has been shown by the reports of Brown[3] and Turk.[4] The wave of enthusiasm that follows the description of any new and interesting disease has caused it to be searched for more carefully and found more often than it would have been otherwise. One cannot but wonder if the enthusiasm of the searchers does not at times carry them beyond the warranted conclusions, particularly in those cases without autopsy. Atypical states of well-known though uncommon conditions are reported as one of the newer clinical entities. In a review of the numerous cases of agranulocytic angina recently reported, there have appeared not a few that have made the writer believe that the reporter's interest in the new condition has clouded the clinical and laboratory findings that really point to a supposedly less interesting diagnosis. With the realization that this has probably taken place in some interpretations, the following case is reported to impress the fact that, though new diseases of the utmost interest may be discovered, the old diseases must be given due recognition; and further, that any conclusion drawn from a case that has not had a postmortem examination must be made very conservatively. For even when there is an autopsy to complete the study of the case, the diagnosis and the pathologic processes involved are often still clouded by our own lack of knowledge, especially in diseases that primarily involve the hemolytopoietic system.

Case Report. E. L., a white male, married, aged 32 years, was admitted to the hospital on the service of Dr. F. J. Dever on December 22, 1931. The patient's condition was too critical to permit taking a history directly from him and the following history was obtained from his wife. About 6 weeks previous to admission, the patient returned from work feeling tired and weak. He went to bed early, but was awakened from sleep by an attack of acute abdominal pain. His wife stated that his abdomen was much distended. He received medical attention but no definite diagnosis was made. From then on he complained of general weakness. Three weeks before admission he began to notice a bleeding from his gums, a constant "oozing," which medical treatment did not control. Refusing to go to a hospital, he became progressively weaker, but was not confined to bed. Five days before admission he began to complain of a sore throat, which three days later had progressed to a peritonsillar abscess which was lanced with some relief. He became rapidly worse and was admitted to the hospital in a semistuporous condition. His wife was unable to give any noteworthy information about his past medical history.

Physical Examination (Dr. H. W. Wright). The patient is a fairly well nourished adult male who appears to be desperately ill and very anemic. He continually spits up bloody material and breaths with great difficulty. Scalp is negative. Eyes: pupils react poorly; equal in size. The ears are negative. Mouth: there is a constant bloody oozing from the gums. The throat is extremely red, swollen and ulcerated with purpuric spots on the roof of the mouth. Neck: the lymph nodes are enlarged. The lungs are negative. Heart: the rate is rapid but regular; the sounds are of poor quality. The abdomen is negative; spleen not palpable. The extremities are negative. Skin: there are ecchymotic spots over the chest and arms.

FIG. 1. FIG. 2.

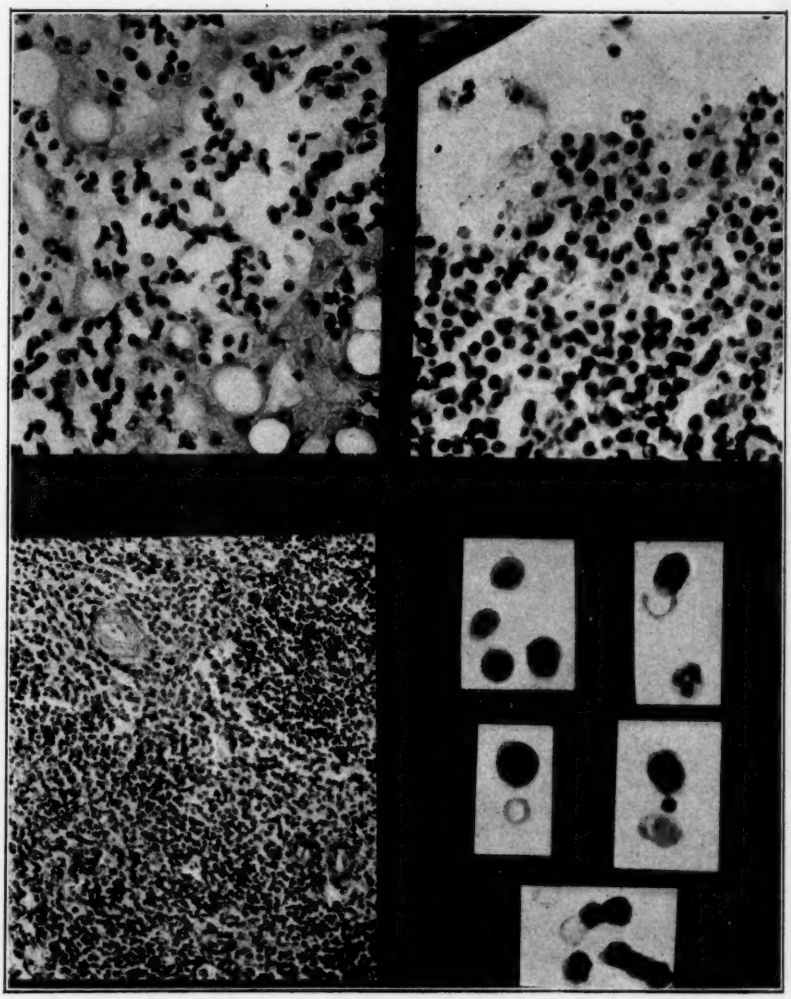

FIG. 3. FIG. 4.

FIG. 1.—Liver, showing infiltration of lymphocytes and fatty infiltration of liver cells. 408 ×.

Fig. 2.—Bone marrow, showing widespread lymphocytic infiltration. 560 ×.

FIG. 3.—Spleen. Central artery with loss of normal structure of surrounding Malpighian body. 156 ×.

FIG. 4.—Blood smear (peroxidase stain). Retouched photographs. *A*, two lower cells are lymphocytes; two upper cells are erythrocytes; *B*, lower cell is a neutrophil; *C* and *D*, upper cells are lymphocytes; *E*, 4 lymphocytes. Peroxidase granules do not stain. 900 ×.

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Eye grounds (Dr. G. E. deSchweinitz) show a widespread retinitis with every type of hemorrhage, old and fresh. The optic disks are pale. There is no optic neuritis or choking of the disks. Where visible, the arteries and veins appear normal in size and color. There are some areas where there is a red rim and a white center which is suggestive of lymphatic leukemia.

Progress and Treatment. The patient received general supportive treatment, local antiseptics to the throat, and a blood transfusion. His temperature remained between 104° and 105° F., his pulse around 135 and his respirations remained around 35. He grew progressively worse and died 3 days after admission.

Laboratory Findings. Urine: faint trace of albumin with an occasional hyaline cast. Coagulation time, 4 minutes. Blood urea nitrogen, 15 mg. per 100 cc. Throat culture: staphylococci with an occasional streptococcus. Blood culture, no growth. Blood counts are recorded in the following table:

Date.	December 22.	December 23 (9 A.M.).	December 23 (3 P.M.).	December 24.
Red cells (millions)	1.3	....	1.4	1.3
Hemoglobin (gm. per 100 cc.)	3.4	....	4.7	2.1
Leukocytes	19,000	18,000	7,700	6,700
Neutrophils:				
Number	2,100	700	380	400
Per cent	11	4	5	6
Lymphocytes:				
Number	17,000	17,000	6,600	6,100
Per cent	89	95	85	91
Monocytes:				
Number	....	....	770	134
Per cent	....	....	10	2
Reticulocytes (per cent)	....	....	1	

The differential smear showed the white cells to be made up mostly of mature lymphocytes. The percentage of monocytes, which in one count reached 10 per cent of the leukocytes, confirms the low percentage of young polymorphonuclear forms, for young forms if present would probably have been classified with these large mononuclear cells. The peroxidase stain was negative on all granulocytic cells making the identification of myelocytes inaccurate.

Autopsy (limited to the abdomen). General examination showed a pale, white, fairly well-nourished male with numerous ecchymotic spots of the skin, most pronounced on the extremities. Lymph nodes slightly enlarged. The liver (2500 gm.) is very pale, the surface smooth and regular, the cut surface not showing any masses or irregularities. The gall bladder does not show any gross abnormalities. The pancreas appears normal. The spleen (400 gm.) is pale and soft, the surface smooth and regular; the cut surface rather pale, grayish and homogeneous. The follicles cannot be seen. The kidneys are both enlarged, very pale and flabby. Both kidneys contain several hematomata, 0.5 to 3 cm. in diameter, some of which protrude into the pelvis. The cortex and medulla are poorly defined. The gastrointestinal tract shows an occasional petechial hemorrhage. The mesenteric and omental lymph nodes are not increased in size.

It was not until the microscopic sections were examined that a definite diagnosis could be made. These all showed the typical changes found in lymphatic leukemia. The lymphocytic infiltrations were of course not as widespread as would be found in a case of longer standing.

Pathologic Histology (Abstract). The spleen showed lymphoid hyperplasia with a loss of normal architecture. In areas vestiges of Malpighian corpuscles could be found around the arteries, but these appeared to melt into the surrounding tissue without any definite boundary. The bulk of

the tissue appeared to be made up almost entirely of adult lymphocytes. There was very little blood in the organ; in some areas there were scattered blood cells in the venous sinuses. Polymorphonuclear leukocytes could only be found after prolonged search. The liver showed fatty infiltration with lymphocytes scattered between the liver cells and massive collections around the portal canals. A mesenteric lymph node showed a uniform hyperplasia of lymphocytes with a loss of normal structure and some infiltration into the surrounding fat. The bone marrow showed an overrunning of the tissue with lymphocytes. Young forms of the red cell and granulocytic series were very difficult to find. This explained the lack of ability of these cells to take the peroxidase stain, for the bone marrow was nearly exhausted from the infiltration of the lymphocytes. The kidneys showed the borders of the hematomata to be made up of masses of lymphocytes which infiltrated into the surrounding tissue, making this tissue resemble a lymph node with here and there a renal tubule or glomerulus. The rest of the kidney showed parenchymatous degenerative changes.

Discussion. In reviewing the clinical aspects of this case, we have a young man admitted to the hospital in a critical condition. His fever, pulse, and the condition of his mouth and throat show him to be suffering from a very acute process at the time of admission. Petechial hemorrhages, however, lose a great deal of value in differential diagnosis in acute conditions like this. The whole process appears to have taken place within 6 weeks, while the more severe symptoms are limited to 3 weeks with the first complaint of sore throat 5 days before admission. His clinical picture is much like agranulocytic angina as described by Schultz[1] and Kastlin.[2] Naturally our interest immediately centered around the blood picture, especially the white and differential counts. The white count at the time of admission was 19,000 with the differential showing 11 per cent polymorphonuclears (total, 2100) and 89 per cent lymphocytes (total, 17,000) (an absolute lymphocytosis and an absolute neutropenia). This and the following counts bring out the importance of reporting the cells in actual numbers and doing away entirely with the often misleading and usually useless terms of relative lymphocytosis, relative lymphopenia, etc. The lymphocytes in this count appeared to be mature in form; the polymorphonuclears did not show a shift to the left. The count made the following day showed the neutrophils to have dropped to 700 while the lymphocytes had not shown any appreciable change. The patient was clinically worse than on admission. The afternoon of the second day in the hospital the lymphocytes had decreased to 7700 and the neutrophils to 380 per c.mm. At this time a peroxidase stain was made. It was found that only an occasional neutrophil would show the peroxidase granules and only one granular myelocyte was found after a prolonged search. The cells of both the lymphocytic and granulocytic series still appeared to be mature cells. The unsuccessful peroxidase stain suggests that these cells were being produced by a diseased, inefficient bone marrow. At this time the differential diagnosis lay between an acute lymphatic leukemia and

an agranulocytic angina. If a case of leukemia, the short duration and severe character would point to an acute form where we would have expected the count to be higher with the presence of many immature forms. It is true that the retinal hemorrhages resembled those of a lymphatic leukemia; but these and petechiæ are also found in other blood disturbances. The patient had a neutropenia on admission and up to his death the lymphocytes were dropping in number, which is characteristic of a typical agranulocytosis. At the time of death the patient was diagnosed as a case of agranulocytic angina. If agranulocytic angina is a clinical entity this diagnosis was in error, but if agranulocytic angina is a clinical syndrome the diagnosis was correct, be the cause of this syndrome what it may.

That agranulocytic angina is a clinical entity appears unlikely from the diversified conditions and blood pictures that are reported as occurring with, and probably causing this condition. This syndrome in a modified form, more chronic, has been associated with the administration of drugs derived from benzene (Farley[5]). These cases are not acute and quite often recover. I have seen 3 typical cases, in all of which the blood count went to below 1000. These 3 cases were all fatal. The interesting point of one case was that it developed in an elderly diabetic who had been under close supervision for over a month and at the time of the acute onset was well standardized. Conner *et al.*[6] have reported a series of cases of agranulocytosis in which there appears to be a diversity of etiologic factors and severity of attack. Most investigators report an aplasia of the granulocytic series in the bone marrow, however Fitz-Hugh and Krumbhaar[7] have recently reported a case in which they show that though the patient had a profound leukopenia in the peripheral blood, the bone marrow showed an increase in the forerunners of the granulocytic series, suggesting a maturation defect. It would seem that the conclusion to be drawn from all this diversity of opinion and clinical and postmortem findings is that agranulocytic angina cannot as yet be considered as a clinical entity. It certainly should not be considered a clinical entity until the cases such as the one here reported and other types of neutropenia of known origin have been weeded out. It would further appear that, when a true case of agranulocytosis is found, the altered blood picture is simply a decrease in the granulocytic cells of the blood stream, from either increased destruction or decreased formation, or both. When no definite cause for this condition can be uncovered, it is permissible to diagnose the case as agranulocytic angina; but before this is done a primary cause must be carefully searched for, with the burden of proof resting on the person making the diagnosis of agranulocytic angina.

Summary. 1. Cases other than those that should be classified as agranulocytic angina are not infrequently appearing in the literature under this heading.

2. A case of apparent agranulocytosis in which autopsy showed the cause to be a lymphatic leukemia is reported. Though clinically acute, this case was hematologically a chronic type of leukemia.

3. In the light of this and of cases in the literature, agranulocytic angina is regarded as a syndrome rather than a clinical entity.

REFERENCES.

1. Schultz, W.: Ueber eigenartige Halserkrankungen, Deutsch. med. Wchnschr., 1922, **48**, 1495.
2. Kastlin, G. J.: Agranulocytic Angina, Am. J. Med. Sci., 1927, **173**, 799.
3. Brown, P. K.: A Fatal Case of Acute Primary Infectious Pharyngitis with Extreme Leukopenia, Am. Med., 1902, **3**, 649.
4. Turk, W.: Septische Erkrankungen bei Verkümmerung des Granulozytensystems, Wien. klin. Wchnschr., 1907, **20**, 157.
5. Farley, D. L.: Depressed Bone Marrow Functions from the Arsphenamines (Including a Type of So-called Agranulocytosis), Am. J. Med. Sci., 1930, **179**, 214.
6. Conner, H. M., Margolis, H. M., Birkeland, I. W., and Sharpe, J. E.: Agranulocytosis and Hypogranulocytosis, Arch. Int. Med., 1932, **49**, 123.
7. Fitz-Hugh, T. Jr., and Krumbhaar, E. B.: Myeloid Cell Hyperplasia of the Bone Marrow in Agranulocytic Angina, Am. J. Med. Sci., 1932, **183**, 104.

STUDIES OF DISEASES OF THE LYMPHOID AND MYELOID TISSUES.

V. The Coexistence of Tuberculosis With Hodgkin's Disease and Other Forms of Malignant Lymphoma.

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Ever since Sternberg, in 1898,[1] called attention to the frequent association of tuberculosis and Hodgkin's disease, speculation has been rife as to the etiologic rôle of the tubercle bacillus in this latter disease. An enormous amount of experimental work has been done in an attempt to settle the question, but differences of opinion still exist among competent pathologists.

Several lines of attack may be followed in the investigation of

the problem. The results of animal injection, bacteriologic examination of involved lymph nodes, the tuberculin reaction and the presence or absence of frank tuberculosis in patients dying of Hodgkin's disease, all must be taken into consideration. The results of tuberculin reactions in one series of cases is to be reported.[2] Cultural and animal experiments on the same series will be reported subsequently. The present paper is concerned only with the coexistence of tuberculous lesions and the various forms of malignant lymphoma, including Hodgkin's disease.

Sternberg[1] found that 8 of his 13 autopsied cases of Hodgkin's disease had also tuberculous lesions, and he regarded Hodgkin's disease as a peculiar form of tuberculosis characterized by the formation of a unique type of granulation tissue. Longcope,[3] however, found no tuberculosis in his 4 autopsied cases, and concluded from this and other considerations that one could not assume that tuberculosis is the cause of Hodgkin's disease. He believed that when tuberculosis occurred in combination with Hodgkin's disease it should be regarded as a secondary infection and of no etiologic importance whatever.

Weber[4] acknowledged the frequent association of the two diseases and felt that they were probably more frequently combined in childhood than in adult life, but he, again, regarded the tubercle bacillus as a secondary invader which found in the granulomatous tissue of Hodgkin's disease an unusually favorable soil for active growth.

Yamasaki,[6] who found tuberculosis in 4 of his 6 cases, regarded the tubercle bacillus as a secondary invader, as did Weber.

Lubarsch[5] admitted that the association of the two diseases was too frequent to be accidental, but he was never able to recover tubercle bacilli from his cases. He pointed out, however, that they might be recovered on animal inoculation even though active tuberculosis could not be demonstrated at autopsy. In this he is supported by Pizzini,[7] who frequently produced tuberculosis in guinea pigs inoculated with bronchial lymph nodes from patients dying without any evidence of active tuberculosis.

Lichtenstein[8] found active tuberculosis in 7 of his 18 autopsied cases and healed tuberculosis in 3 more. He appears to be the first author to sharply distinguish between healed and active tuberculosis—a point of no small importance as will be seen later. Lichtenstein reviews the literature most thoroughly, and he concludes from his own studies that the frequency of the association of the two diseases, the intermingling of the lesions microscopically and the production in guinea pigs of tuberculosis when injected with apparently pure Hodgkin's disease nodes justify the opinion that this disease is due to tuberculosis.

Brandt[9] found tuberculosis in 5 of his 14 cases, but he did not ascribe etiologic importance to the bacilli.

Finally, Twort,[10] after a careful consideration of 61 cases, came to the conclusion that "the etiology of lymphogranuloma still remains obscure to us." He could "demonstrate consistently no specific animal or vegetable parasite in the diseased tissues either by direct microscopic examination, cultivation or animal injection." He found, "contrary to what is usually taught," only rare association with tuberculosis—in fact, in only 3 of his 27 autopsied cases did he find evidence of this condition.

One can, therefore, find in the literature opinions that support almost any point of view and the situation is not made more clear by the statement by Lemon,[11] that, on the basis of Roentgen ray examination, in only 8 of his 191 cases was there evidence of tuberculosis.

In view of the conflicting evidence in the literature, it seemed wise to review the material from our own clinics and to compare, furthermore, the incidence of tuberculosis in Hodgkin's disease with that in other types of malignant lymphoma—lymphocytoma, lymphosarcoma, lymphatic leukemia—and in other types of fatal disease, including myelogenous leukemia.

For this purpose all the autopsied cases of malignant lymphoma and myelogenous leukemia at the Boston City Hospital, the Peter Bent Brigham Hospital and the Children's Hospital were studied (151 cases). We are greatly indebted to Dr. S. Burt Wolbach for his kindness in placing his material at our disposal. Only those cases in which complete autopsy was performed were included. In addition, the same data were obtained on 212 unselected cases of cancer of the same age distribution, 50 cases of pernicious anemia and 400 "general autopsy" cases distributed over the same period of years.

The results are tabulated on page 697. The diagnosis of Hodgkin's disease was made according to the usually accepted standards as originally laid down by Dorothy Reed and by Sternberg. The cases were rather evenly distributed throughout the decades of life. It will be noted that 1 case had both lymphatic leukemia and widespread Hodgkin's disease. This case has previously been reported.[12] One case of lymphocytoma also had Hodgkin's disease. These figures, which are not shown in the table for simplicity's sake, do not alter the fact that no active tuberculosis was found in any case of malignant lymphoma with or without lymphatic leukemia except Hodgkin's disease. (Tables 1 and 2.)

From the literature already alluded to above, we find that tuberculosis was found in 30 of the 78 autopsied cases of Hodgkin's disease. The available data do not justify the subdivision of these cases into active and healed tuberculosis, but we can say that 38.5 per cent of the published cases showed some form of the disease. This corresponds very closely indeed with our own figures of 33.3 per cent in 30 cases of Hodgkin's disease.

TABLE 1.—COMBINED REPORTS FROM AUTOPSIES AT THE BOSTON CITY HOSPITAL, THE PETER BENT BRIGHAM HOSPITAL AND THE CHILDREN'S HOSPITAL.

Disease.	Number.	Absent.	Present.	Active.	Healed.	Per cent total tuberculosis.
			Total Tuberculosis.			
General	400	323	77	44	33	19.3
Cancer	212	181	31	12	19	14.6
Hodgkin's	30	20	10	6	4	33.3
Lymphosarcoma	13	9	4	0	4	30.8
Lymphatic leukemia	30	27	3	0	3	10.0
Lymphocytoma	5	4	1	0	1	20.0
Reticulum-cell sarcoma	14	11	3	0	3	21.4
Myelogenous leukemia	50	40	10	5	5	20.0
Myeloma	6	5	1	0	1	16.6
Pernicious anemia	50	42	8	0	8	16.0
			Active Tuberculosis.			
General	400	..	..	44	..	11.0
Cancer	212	..	..	12	..	5.7
Hodgkin's	30	..	..	6	..	20.0
Lymphosarcoma	13	..	..	0	..	0.0
Lymphatic leukemia	30	..	..	0	..	0.0
Lymphocytoma	5	..	..	0	..	0.0
Reticulum-cell sarcoma	14	..	..	0	..	0.0
Myelogenous leukemia	50	..	..	5	..	10.0
Myeloma	6	..	..	0	..	0.0
Pernicious anemia	50	..	..	0	..	0.0
			Healed Tuberculosis.			
General	400	..	..	..	33	8.3
Cancer	212	..	..	..	19	9.0
Hodgkin's	30	..	..	..	4	13.3
Lymphosarcoma	13	..	..	..	4	30.8
Lymphatic leukemia	30	..	..	..	3	10.0
Lymphocytoma	5	..	..	..	1	20.0
Reticulum-cell sarcoma	14	..	..	..	3	21.4
Myelogenous leukemia	50	..	..	..	5	10.0
Myeloma	6	..	..	..	1	16.6
Pernicious anemia	50	..	..	..	8	16.0

TABLE 2.—DISTRIBUTION IN ORGANS OF LESIONS OF ACTIVE TUBERCULOSIS AND HODGKIN'S DISEASE.

Autopsy No.	Tuberculosis alone.	Hodgkin's disease alone.	Hodgkin's disease and tuberculosis.
A 23–54	Lung, spleen, adrenal, intestine, brain	Liver	Lymph nodes.
A 28–319	Lung, pancreas, intestine, marrow	0	Spleen, liver, lymph nodes.
A 28–148	Lung	Stomach	0
U 28–18	Intestine	Liver, spleen, marrow, lymph nodes	Lung.
A 28–246	Lung, spleen, adrenal, intestine	Liver	Lymph nodes.
A 30–253	Intestine	Liver, adrenal, lymph nodes, marrow	Spleen.

Carlson and Bell[13] published an analysis of tuberculosis in cancer, heart disease and general autopsies. Our figures agree closely with theirs. In general autopsies we found 19.3 per cent total tuberculosis as against their 17.3 per cent, and in cancer we found healed tuberculosis in 9 per cent of the cases against their finding of 8.6 per cent. These statistical similarities are brought out to indicate that the accuracy with which tuberculosis was diagnosed postmortem in our series approximates that of another large clinic.

From the data obtained in our own series it would appear:

1. That the percentage of total tuberculosis, both healed and active, is significantly greater in Hodgkin's disease (33.3) than in other types of lymphoma (5.3) or in cancer (14.6) or general autopsies (19.3).

2. That the percentage of active tuberculosis in Hodgkin's disease (20) is very markedly greater than in the other types of lymphoma (0) or in pernicious anemia (0), cancer (5.7) or general autopsies (11).

3. That the percentage of healed tuberculosis does not materially differ in the various types of lymphoma.

4. That while cases of myelogenous leukemia have an approximately normal percentage of active tuberculosis, we found no case of pure lymphoma associated with active tuberculosis. In previous studies this fact has not been emphasized, if, indeed, it has been noted at all. It would appear to be just as significant as the association of tuberculosis with Hodgkin's granuloma.

We have found, therefore, an incidence of active tuberculosis in Hodgkin's disease far in excess of that in either the general autopsies or in other types of malignant lymphoma. It is generally acknowledged that the pathologic picture of Hodgkin's disease is distinct. If it be assumed that the tubercle bacillus is of etiological importance in Hodgkin's disease, one of two postulates must be made. Either the tubercle bacillus is not of the usual pathogenicity or the host differs in some way so that the conventional tubercle bacillus produces a fatal granuloma rather than the usual tuberculous process. If the former be the case we are faced with the very unusual fact that a large number of these Hodgkin's disease cases are invaded by both types of tubercle bacilli. If the latter assumption be made we must explain why the host reacts in two different ways to the same organism at the same time. It would seem to us that the frequent association of the two diseases indicates merely that the one predisposes to the other or that the same constitutional type is subject to both.

The explanation of the extremely low incidence of active tuberculosis in other forms of malignant lymphoma is difficult. It may possibly lie in the presence throughout the body of very large numbers of lymphocytes—well-known antagonists of the tubercle bacilli.

Conclusions. Hodgkin's disease has a much greater incidence of associated tuberculosis than is found in general autopsies, pernicious anemia or cancer.

In our experience malignant lymphoma of other types (not Hodgkin's disease) is never associated with *active* tuberculosis. This latter point has hitherto not been emphasized.

REFERENCES.

1. Sternberg, C.: Ueber eine eigenartige unter dem Bilde der Pseudoleukämie verlaufende Tuberkulose des lymphatischen Apparates, Ztschr. f. Heilk., 1898, **19**, 21.

2. In press.

3. Longcope, W. T.: On the Pathology of Hodgkin's Disease with a Report of a Series of Cases, Bull. Ayer Clin. Lab. Penn. Hosp., 1903–1904, **1**, 4.

4. Weber, F. P.: Acute Cases of Hodgkin's Disease (Lymphadenoma) and the Diagnosis of the Disease from Syphilis, Tuberculosis and Atypical Leukemia, St. Barth. Hosp. Rep., 1908, **43**, 81.

5. Lubarsch, O.: Ueber Lymphogranulomatose, Berl. klin. Wchnschr., 1918, **55**, 708.

6. Yamasaki, M.: Zur Kenntnis der Hodgkinschen Krankheit und ihres Ueberganges in Sarkom, Ztschr. f. Heilk., 1905, **25**, 269.

7. Pizzini, D. L.: Tuberkelbacillen in den Lymphdrüsen Nichttuberkulöser, Ztschr. f. klin. Med., 1892, **21**, 329.

8. Lichtenstein, A.: Untersuchungen über die Aetiologie der Lymphogranulomatosis (Sternberg), Frankfurt. Ztschr. f. Path., 1921, **24** (Ergnzngshft.), 529.

9. Brandt, M.: Beitrag zur pathologischen Anatomie der Lymphogranulomatose, Virchow's Arch. f. path. Anat., 1929, **272**, 400.

10. Twort, C. C.: Aetiology of Lymphadenoma; Summary of 6 years Researches, J. Path. and Bact., 1930, **33**, 539.

11. Lemon, W. S.: Tuberculosis as an Etiologic Factor in Hodgkin's Disease. A Historical Review, Am. J. Med. Sci., 1924, **127**, 178.

12. MacMahon, H. E., and Parker, F., Jr.: Case of Lymphoblastoma, Hodgkin's Disease and Tuberculosis, Am. J. Path., 1930, **6**, 367.

13. Carlson, H. A., and Bell, E. T.: Statistical Study of Occurrence of Cancer and Tuberculosis in 11,195 Postmortem Examinations, J. Cancer Res., 1929, **13**, 126.

A VALUABLE SIGN IN THE DIFFERENTIAL DIAGNOSIS OF ACUTE ABDOMINAL MALARIA.

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During 5 years' hospital surgical practice in the Caribbean littoral (Colombia, Panama and Guatemala), the writer has kept records of all cases of malaria or suspected malaria in which vomiting or other acute abdominal symptoms were prominent. A tropical surgeon had early admonished that confusion and error marked the efforts of surgeons from temperate zones to differentiate acute abdominal catastrophes demanding surgical intervention from the more violent abdominal manifestations of tropical malaria.

In examining the records, it is enlightening to find that they total only 25 cases, compiled in regions where the malaria morbidity is

enormous (the community thick-film positive index being not infrequently as high as 35 per cent) and the malaria death rate probably as high as that in any part of the world. Of these cases, 16 yielded positive smears for malaria parasites in the peripheral blood, 6 had negative smears but have been classified as cases of malaria because of response to quinin and other indications to be discussed, and 3 were diagnosed as malaria on admission but proved to be acute surgical cases. In addition to these 3, of 16 patients with positive smears, 1 had an acute surgical lesion (spontaneous rupture of the spleen). It is evident, therefore, that the problem of differential diagnosis between abdominal malaria and the surgical conditions does not present itself with great frequency in these malaria-infested regions.

Presence of Occult Blood in Vomitus and Absence of Involuntary Rigidity Characteristic of Abdominal Malaria. Two clinical signs of great significance characterize the cases of abdominal malaria under discussion. These are the presence of macroscopic or occult blood in the gastric contents or vomitus during acute paroxysms of the disease, and absence of the *"sine qua non"* of peritoneal inflammation —involuntary abdominal rigidity. Of the 21 cases of malaria, all but 3 (85 per cent) showed blood in the gastric secretion. Of the 3 cases without this sign, 2 had been under quinin therapy for several days before the gastric examination was made, and the third, although vomiting had occurred for 8 days, had no other abdominal signs and probably did not have an abdominal form of malaria. In none of the cases was there actual involuntary muscular rigidity of the abdomen. The importance of these diagnostic signs (particularly the finding of occult blood) has not previously been emphasized. James,[1] Deaderick and Thompson,[2] Byam and Archibald,[3] Manson-Bahr[4] and Masters[5] have reported the finding of blood in the gastric contents or stools of malarial sufferers. These writers, however, ascribe this sign as a characteristic of the algid type of malaria, rather than of the abdominal variety. James describes the finding of "small hemorrhages into the tissues of the mucosa and villi" and "patches of necrosed epithelium." Businco[6] attributed the gastralgia and bloody vomitus observed in some cases of chronic malaria to erosion of gastric mucosa, while Castellani and Chalmers[7] note the similarity of these symptoms to those of carcinoma.

Absence of Rigidity in Abdominal Malaria. The writer has never observed true abdominal rigidity in uncomplicated cases of the type under discussion. In this assertion he is not supported by some observers. Demjanow[8] in reporting upon 7 cases of "malarial appendicitis" found rigidity in all. None of these cases, however, were operated upon, so that confirmation of the diagnosis is lacking. In 2 of the patients who died of malaria, postmortem microscopic examination of the appendices revealed thrombi of malarial pigment, enlargement of the lymphatic structures and infiltration of the sub-

mucosa and mucosa. Obviously, pathologic changes of this nature predispose the appendix to gangrene or pyogenic infection. Under such circumstances, one should not hesitate to operate if pain and rigidity are persistent, the leukocyte count is considerably increased, or nonfilamented neutrophils make their appearance in the peripheral blood in significant numbers. DePenning[9] reports 2 cases of supposed malarial appendicitis with slight rigidity, unoperated. Castellani and Chalmers (*loco citato*) have also observed rigidity in malarial appendicitis.

It is significant that these claims for rigidity in abdominal malaria are all based upon cases of appendiceal involvement. Preëxisting or impending bacterial invasion of the appendix cannot be excluded in such reports.

Sporulation of malaria parasites in other abdominal viscera, notably in the liver, pancreas and spleen, is not definitely on record as a cause of rigidity. Cignozzi[10] states that the liver and gall bladder are almost constantly attacked by malaria. Acute gastrointestinal manifestations of this disease are discussed by Biddan,[11] Martini,[12] Uduondo with Sanguinetti,[13] and Jahavery.[14] None of these investigators report the finding of abdominal rigidity, even in cases of malarial appendicitis. The presence of blood in the stools is frequently noted. There are no references, however, to the test for occult blood in vomitus or material obtained for gastric analysis. Uduondo attests the finding of necrosis of lymph follicles and Peyer's patches at autopsy. According to this writer, the response to test meal in malaria is characterized by hypochlorhydria, bile and mucus. Examinations for occult blood were not performed. (An interesting parallel is seen in Businco's description of the typical radiographic stigmata of chronic malaria—atonic gastrectasis, ptosis of the pylorus and hypomotility.)

Rieux[15] lists the following conditions as most liable to be confused with abdominal forms of malaria: appendicitis, biliary infections, urinary sepsis and complications of dysentery and typhoid fever. He calls attention to the value of the therapeutic test with quinin, and states that there are no "quinin resistant" parasites. It is well recognized, however, that overwhelming malarial infections respond indifferently to quinin.

Abdominal Forms of Malaria With Occult Blood in the Vomitus. The following cases are characteristic in history, symptomatology, physical findings and examination of gastric secretion.

Case Reports. CASE 3.—Native male, aged 34 years, had fever, vomiting and pain in his spleen for 2 days. He was slightly jaundiced. Examination of his abdomen was negative except for moderate splenic enlargement. The admission temperature was 101° F. Blood count disclosed erythrocytes 2,410,000, hemoglobin 40 per cent, leukocytes 8100. The vomitus was bile-stained and yielded a positive test for occult blood. Examination for malaria parasites revealed estivo-autumnal crescents.

TABLE 1.—ANALYSIS OF CASES REQUIRING DIFFERENTIAL DIAGNOSIS BETWEEN ABDOMINAL MALARIA AND ACUTE SURGICAL LESIONS.

Case.	Status.	Symptoms.	Duration.	Physical signs.	Malaria smear.	Preliminary diagnosis.	Course.	Gastric contents.	Revised diagnosis.
1	Native, aged 19	Fever, vomiting, abd. pain	7 days	Generalized abd. tenderness	E. A. rings	Malaria	Recovered	Occult blood xx Epith. cells xx Leukocytes x R. B. C. x Bile xx	E. A. malaria.
2	Native, aged 31	Chills and fever, abd. pain, vomiting	4 months	Enlarged liver and spleen	E. A. rings	Malaria	Recovered	Occult blood xx R. B. C. x Bile x	E. A. malaria.
3	Native, aged 34	Fever, vomiting, pain in spleen	2 days	Anemia; jaundice; enlarged spleen	E. A. crescents	Malaria	Intramusc. quinin; relapse 6th dy.; transfusion; recov.	Occult blood x Bile x	E. A. malaria.
4	Native, aged 17	Fever, vomiting, abd. pain	2 weeks	Enlarged spleen	E. A. rings	Malaria	Recovered	Occult blood x Mucus x	E. A. malaria.
5	Negro, aged 22	Fever, abd. pain, vomiting, constipa.	3 days	Incarcerated inguinal hernia	E. A. rings	Strangulated hernia; peritonitis	Recovered	Occult blood xxx Bile x	E. A. malaria.
6	Native, aged 50	Fever, vomiting	3 days	Enlarged spleen	Tertian rings	Malaria	Recovered	Occult blood x Epith. cells xxx Leukocytes xx R. B. C. x Bile x	Tertian malaria.
7	Native, aged 34	Fever, vomiting, abd. pain	4 days	Tenderness upper abd., prostration, cyanosis	E. A. rings	Malaria	Recovered	Occult blood x Leukocytes xx Mucus xxx Bile x	E. A. malaria.
8	Native, aged 21	Headache, vomiting, fever	5 days	Medical shock; abd. tenderness	E. A. rings and crescents	Malaria	Recovered	Occult blood x Mucus x Leukocytes x	E. A. malaria.
9	Native, aged 15	Fever, cough, abd. pain	2 days	Coryza	E. A. rings	Malaria	Recovered	Occult blood xx Leukocytes x Mucus xx	E. A. malaria.
10	Native, aged 38	Fever, vomiting	5 days	Prostration	E. A. rings	Malaria	Recovered	Occult blood x Leukocytes x Mucus x Bile x	E. A. malaria.
11	Native, aged 28	Fever, headache, vomiting	3 days	Abd. tenderness; collapse	E. A. rings	Malaria	Recovered	Occult blood x Leukocytes x Mucus x Bile x	E. A. malaria.
12	Native, aged 31	Fever, vomiting, abd. pain	5 days	Palpable spleen	E. A. rings	Malaria	Recovered	Occult bloodxxxx	E. A. malaria.

12	Native, aged 31	Fever, vomiting, abd. pain	5 days	Palpable spleen	E. A. rings	Malaria	Recovered	Occult bloodxxxx Bile x	E. A. malaria.

TABLE 2.—CLINICAL MALARIA WITH NEGATIVE BLOOD SMEAR.

Case.	Status.	Symptoms.	Duration.	Physical signs.	Malaria smear.	Preliminary Diagnosis.	Course.	Gastric contents.	Revised diagnosis.
13	Native, aged 18	Fever, epigastric pain, vomiting	6 days	Epigastric tenderness	Negative	Malaria	Recovered	Occult blood xxx Leukocytes xx Epith. cells xx Bile xxxx	Malaria.
14	Native, aged 29	Fever, chills, vomiting	8 days	Enlarged spleen; anemia	Negative	Malaria	Transfusion; recovered	Occult blood x Bile x	Malaria.
15	Native	Fever, abd. pain, vomiting	3 days	Abd. tenderness and distention; jaundice; prostration	Negative	Malaria or yellow fever	Death 2d day. Aut.: toxic hepatitis, enlarged spleen, neg. smears from liver and spleen	Occult blood x	Malaria.
16	Italian, aged 41	Fever, chills, pain in back and loins	1 month	Negative	Negative	Malaria	Hemoglobinuria on 3rd day; recovered	Occult blood x	Blackwater fever.
17	Native, aged 29	Chills, fever, vomiting	1 day	Negative	Negative	Malaria	Recovered	Occult blood x	Malaria.
18	Native, aged 18	Fever, abd. pain, vomiting	6 days	Abd. tenderness; enlarged spleen; prostration	Negative	Malaria	Algid type; T. 95.6°; constant vomiting 12 hours; active stimulation; recovery	Occult blood xxx Leukocytes x Mucus x	Malaria.
				MALARIA WITHOUT OCCULT BLOOD					
19	Negro, aged 24	Fever, chills, vomiting, abd. pain	5 days	Negative	E. A. rings	Malaria	Recovered	Negative	E. A. malaria.
20	Native, aged 33	Fever, abd. pain, vomiting	4 weeks	Enlarged spleen; anemia	Negative	Malaria	Recovered	Negative; had taken quinin for 6 days	Malaria.
21	White, aged 28	Fever, abd. pain, vomiting	8 days	Negative	E. A. rings and crescents	Malaria	Recovered	Negative	E. A. malaria.

TABLE 3.—SURGICAL CASES.

Case.	Status.	Symptoms.	Duration.	Physical signs.	Malaria smear.	Preliminary diagnosis.	Course.	Gastric contents.	Revised diagnosis.
22	Negro, aged 55	Vomiting, abd. pain	3 days	Abd. distention and tenderness	Negative	Malaria	Diag.: acute intes. obstruction; operation: car. of pylorus with obstruction and metastasis. Died	Occult blood xx	Carcinoma of pylorus.
23	Native, aged 19	Fever, vomiting	3 days	Abd. distention and tenderness; compound fracture of tibia, not grossly infected	Negative	Malaria	Fever; vomiting ascarides until death on 2d day. Aut.: anemia, dil. of left auricle, splenic hypertrophy; 22 live ascarides; no intest. obstruction	Occult blood xxx Epith. cells x Bile xx	Ascariasis; septicemia.
24	Native, aged 19	Vomiting, pain in spleen, weakness	4 hours	Abd. distention; dullness in flanks; tender spleen; intra-abd. hemorrhage	E. A. rings	Malaria	Splenectomy for rupture; autotransfusion; death from shock and hemorrhage	Negative	Spont. rupt. of spleen; E. A. malaria.
25	Native, aged 25	Abd. pain, vomiting	3 days	Abd. distention, rigidity and mass	Negative	Malaria	Treated for malaria for 3 days; repeated purging. Aut.: perf. of 2 typhoid ulcers; general peritonitis	Negative	General peritonitis; perforation of typhoid ulcers.

The patient was given 4 intramuscular injections of quinin dihydrochlorid of 1 gm. each at 6-hour intervals. Thereafter, 1 gm. was administered by mouth at similar intervals. On the fifth hospital day the patient's temperature became normal, and the dosage of quinin was reduced to 1 gm. 3 times daily. Six days later, while 3 gm. of quinin sulphate was still being taken daily by mouth, the patient again became feverish and irrational. Vomiting recurred, with the vomitus still showing occult blood. The urine now contained 0.5 per cent albumin but no hemoglobin. No malaria parasites were found in the circulating blood. Because of the persistent occult blood reaction, intramuscular injections of quinin were resumed, and the temperature became normal on the third day. The blood count now disclosed erythrocytes of only 2,100,000 and hemoglobin of 15 per cent. Transfusion of 200 cc. of citrated blood was performed and recovery ensued without further complications.

This case presents three illustrative features: (1) enormous resistance of a malarial infection to quinin therapy; (2) the misleading finding of only a few estivo-autumnal crescents in the thick film; (3) recurrence of a severe malarial infection, with massive blood destruction, while quinin treatment was being practised. This was corroborated by the finding of occult blood in the vomitus while the blood smear remained negative.

CASE 5.—Negro male, aged 22 years, was admitted with a history of fever and chills for 3 days, accompanied by generalized abdominal pain, most severe in the upper quadrants, vomiting, constipation and headache. The temperature was 104° F, and slight delirium was evident. The admitting physician had made the diagnosis of strangulated inguinal hernia, with peritonitis. Abdominal examination was negative, except for the presence of a slightly enlarged and tender spleen. The hernia was incarcerated (probably as a result of constant vomiting), but was reduced without difficulty. Estivo-autumnal rings were found in the thick film. The vomitus was bile-stained and contained macroscopic blood. Two days later, after quinin treatment, a test meal yielded bile, no occult blood, and occasional leukocytes and epithelial cells. The temperature was normal and vomiting had stopped on the second day.

Inferential Diagnosis of Malaria by Presence of Occult Blood. The clinical existence of acute forms of tropical malaria with one or more negative blood smears is not uncommon. Elucidation of the reasons for the occurrence of this paradox does not lie within the scope of the present paper. Intermittent or irregular self-treatment with quinin is probably the commonest cause of failure to find parasites in the peripheral blood. A certain percentage of such cases, in which acute manifestations of sporulation in the abdominal viscera make their appearance, may be diagnosed tentatively as malaria by the finding of occult blood in the vomitus. The correctness of this interpretation is signified by the course of events in the following case records:

CASE 14.—Native male, aged 28 years, was reputed to have had fever, chills and vomiting for 8 days. His condition appeared very unfavorable. He was vomiting constantly. The erythrocyte count numbered only 1,800,000, with hemoglobin 20 per cent. Urine examination was negative, as were both thick and thin blood films. The spleen was considerably

enlarged, but other abdominal signs were absent. Fever of 103° F. was experienced.

Analysis of the vomitus revealed occult blood and bile. The patient was given 0.5 gm. doses of quinin dihydrochlorid with adrenalin 0.7 cc. Slight improvement was noted the next day, but blood was still present in the vomitus. Horse serum failed to check this diapedesis. Transfusion of 400 cc. of citrated blood had the desired effect, however. On the sixth day the temperature became normal.

CASE 15.—Native male, aged 19 years, had fever, pain in the abdomen and vomiting for 3 days before admission. This was a recurrence of similar symptoms which had existed intermittently for a number of weeks, and had been treated with small doses of quinin.

The patient was extremely prostrated and jaundiced. His abdomen was universally tender and slightly distended. Blood examination for malaria parasites was negative. The vomitus contained occult blood, but was not of the character observed in yellow fever. Urine examination was negative save for the presence of bile pigments. The temperature rose to 104.2° F.

Active stimulation and quinin injections were utilized. The patient vomited copiously before dying on the second hospital day. Postmortem examination was entirely negative save for the manifestations of jaundice, toxic hepatitis, and the presence of splenic enlargement grade two. Smears from the liver and spleen failed to reveal malarial parasites. Smears from bone marrow were not made. Weil's disease, yellow fever and septicemia suggest themselves as alternative diagnosis. The history of this patient before coming to the hospital was that of malaria. On two previous admissions within a year he had positive blood smears.

Abdominal Malaria Without Occult Blood. Three cases of malaria with acute abdominal symptoms were observed to have the gastric secretion free of occult blood. In 2 of these, the analysis was made after several days of quinin treatment.

Nonmalarial Surgical Cases With and Without Occult Blood. Four additional cases are recorded which illustrate the fallibility and also the usefulness of the occult blood test in distinguishing surgical from malarial abdominal cases. In all of these, the preliminary diagnosis upon admission was malaria.

Spontaneous Rupture of the Spleen. CASE 24.—Native male, aged 19 years, was seen in consultation 18 hours after admission in the hospital. Because of his collapsed condition no direct history was obtainable. He had been picked up in an apparently fainting condition in the shop where he was at work. He was not seen to have been struck or injured, and had appeared to be in ordinary health.

On entering the hospital, it was noted that the patient's spleen extended below the anterior superior iliac spine. The patient complained of pain in the splenic area, nausea and weakness. The temperature was 98.1° F.; pulse, 94; respiration, 24. Blood examination revealed estivo-autumnal rings. Routine treatment for malaria was instituted. Shortly after admission the patient vomited bile-stained fluid. This was negative for occult blood.

When seen by me, the patient was restless; the pulse, 130; temperature, 97.4° F.; respiration, 30. The extremities were cold. There was considerable abdominal distention, and dullness could be percussed in both flanks. Pain in the spleen was constant and severe. Vomiting had occurred on two succeeding occasions, the vomitus in each case being free of occult blood. A needle was inserted into the abdominal cavity in the left iliac region, and 20 cc. of dark blood were aspirated. The diagnosis of splenic rupture was made. On the operating table, intravenous infusion was started before the abdomen was opened. A large stellate rent was disclosed

on the diaphragmatic surface of the spleen. While large quantities of blood were retrieved from the abdomen, citrated and infused, the spleen was freed with difficulty from numerous adhesions, and removed. The patient succumbed to shock and hemorrhage. Delay in operating probably caused this fatality.

Conclusions. 1. The great majority of sufferers from tropical malaria with acute abdominal symptoms in this study were infected with estivo-autumnal parasites (93 per cent).

2. Of this number, a high percentage (85 per cent) revealed positive tests for occult blood in the vomitus or gastric contents. The finding of occult blood was of considerable value in establishing the diagnosis of abdominal malaria.

3. The distinction of acute abdominal malaria from acute surgical lesions of the abdomen rests principally upon physical signs, of which the most important is absence of rigidity in malaria.

REFERENCES.

1. James, S. P.: Malaria at Home and Abroad, John Bale Sons, London, 1920, p. 140.
2. Deaderick, W. H., and Thompson, L.: Endemic Diseases of the Southern States, Philadelphia, W. B. Saunders Company, 1916, p. 116.
3. Byam, W., and Archibald, R. J.: The Practice of Medicine in the Tropics, Henry Froude, Hodder & Stoughton, London, 1922.
4. Manson-Bahr, P. H.: Tropical Diseases, Cassell & Co., London, 1921, p. 45.
5. Masters, W. E.: Essentials of Tropical Medicine, John Bale Sons, London, 1920, p. 99.
6. Businco, O.: Le Gastro-enteropatie dei Malarici Chronici, Riforma med., 1929, **45**, 1142.
7. Castellani, A., and Chalmers, A. J.: A Manual of Tropical Medicine, London, 1919, p. 1177.
8. Demjanow, G. S.: Ueber die Appendicitis malarica, Centralbl. f. Bakt., 1926, **100**, 348.
9. De Penning, H.: Malaria and Appendicitis, Brit. Med. J., 1928, **1**, 53.
10. Cignozzi, O.: Malaria and Gallstones, Abs., J. Am. Med. Assn., 1919, **85**, 934.
11. Biddan, I.: Perniciosa malarica che simula una peritonitis acuta, Gazz. de Osp., 1929, **50**, 1326.
12. Martini, V.: Colica appendicolare de origine malarica, Cultura Med. Mod., 1930, **9**, 101.
13. Uduando, C., and Sanguinetti, L.: Gastroenteropatias Paludicas, Los progresos de la Clinica, 1926, **23**, 623.
14. Jhaveri, M.: The Gastro-intestinal Type of Malaria, Indian Med. Gaz., 1926, **61**, 26.
15. Rieuz, J.: Le Pseudo Paludisme, J. rev. gén. de chir. et de thérap., 1928, **42**, 369.

A STUDY OF THE PATHOGENESIS OF MYOCARDIAL FIBROSIS ("CHRONIC FIBROUS MYOCARDITIS").

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IT has long been known that in many severe infectious diseases such as typhoid fever, diphtheria and scarlatina, acute focal myocarditis may be present; but it seems important to determine

whether these acute infections play any rôle in the production of the myocardial scars seen frequently at autopsy. O'Hare[1] states that Assman and other German writers, Osler and most authors of current textbooks on the subject believe that acute infections, especially diphtheria and rheumatic fever, are common causes of chronic myocarditis, and Fahr[2] finds that the general practitioner believes that foci of infection are largely responsible for chronic muscular incompetency of the heart in which there is no other obvious cause. Brooks,[3] from the analysis of a large number of autopsies, ascribes the scarring of the muscle to a great variety of causes.

There has been much misunderstanding of the term "chronic myocarditis." For the clinician it means myocardial insufficiency, as evidenced by the poor quality of the heart sounds and decompensation; while the pathologist uses it to describe areas of fibrous tissue in the myocardium. A more accurate term would be "scarring of the myocardium" or "myocardial fibrosis."

Material. The material for this study consisted of 1000 consecutive autopsies (7000 to 7999) from this department, of which 110 described areas of scar tissue in the myocardium. Various changes were found in the myocardium in 81 other cases but there was no evidence available to show that these might ultimately be related to myocardial scarring. The only useful material for analysis was that in which actual scarring was found and the following is an attempt to recognize the course of events in those 110 cases.

This group, in which the scarring varied in extent from fibrous areas seen only under the microscope to great scars involving a large part of the left ventricle, included especially arteriosclerotic and syphilitic cases. A tabulation shows the following:

TABLE 1.—ANALYSIS OF 110 CASES OF MYOCARDIAL SCARRING.

59	Generalized arteriosclerosis: 6 with syphilis not involving heart or aorta, 52 showing advanced coronary sclerosis, 3 with normal coronaries and 4 with no report.
24	Syphilitic aortitis: 15 of these showed coronary sclerosis, 7 had normal coronaries and 2 with no report, 2 also with arteriosclerosis and hypertension.
15	Rheumatism: of these 2 had coronary sclerosis, 12 normal coronaries and 1 with no report.
12	Miscellaneous: 3 had a Streptococcus viridans endocarditis, of which 2 were on a basis of old rheumatism but with normal coronaries, 1 had chronic aortic endocarditis, probably rheumatic, 4 had generalized tuberculosis, 1 chronic nephritis and there were 3 others in which the coronaries seemed unchanged or attracted no notice.

Thus, in 110 cases, 98 were plainly associated with arteriosclerosis, syphilitic aortitis or rheumatism, while of the 12 others, 3 at least gave evidence of old healed rheumatism, 4 were cases of tuberculosis, 1 chronic nephritis, while 3 were children in whom the process was probably quite different.

It seems that the possible causes of scarring in the myocardium may be classified as follows:

1. Focal infectious myocarditis. (*a*) acute; (*b*) chronic.
2. Toxic myocarditis.
3. Interference with the blood supply. (*a*) Thrombosis or embolism; (*b*) ischemic necrosis from slow reduction of blood supply.

Focal Infectious Myocarditis. In the present series of 1000 cases the clinical histories of those with and without chronic fibrous myocarditis gave, of course, frequent evidence of such infectious diseases as pneumonia, typhoid fever, diphtheria, scarlatina and malaria. Since these were quite as common in the 890 cases in which there was no scarring, it seems impossible to ascribe the scarring to them in the present series.

In the group recognized as syphilis and rheumatism the question arises as to whether the sclerosis followed a previous focal myocarditis. Warthin,[4] in a series of 41 cases of syphilis, found 36 active lesions in the heart and 32 in the aorta. He defines active lesions as those in which spirochetes or characteristic tissue lesions are present. Brooks,[5] in a series of 50 autopsies on luetic hearts, found changes in 44. Fibroid changes were present in 14, gummata in 5, and true myocarditis with infiltration of leukocytes in 6 cases of which 5 also showed scar tissue.

Of the 24 syphilitic hearts showing myocardial fibrosis in this series, only 6 gave evidence of any infiltration of leukocytes and no spirochetes were found. In 3 cases there was perivascular infiltration and fresh scars were present. In 2, lymphocytes were found about necrotic areas. It seems probable, therefore, that local syphilitic lesions may play a part in producing myocardial scars.

The cases of rheumatic fever present a similar problem as to the pathogenesis of the scar tissue. It is our common experience (MacCallum[6]) that the remains of Aschoff bodies may be recognized for a long time, as scar-like thickenings of the adventitia and periadventitial tissue about the branches of the coronary arterioles. Occasionally, in the earlier stages, small foci of necrosis of the muscle fibers may be seen but in the end no extensive scarring appears to result and even the perivascular thickenings contract and tend to disappear. Slater[7] quotes Aschoff as stating that he believed they cleared up. Slater himself writes that he believes all myocardial scars in rheumatic heart disease are due either to invasion of the vessel or its constriction following periarterial infiltration (Aschoff bodies) and not primarily to focal myocarditis.* In this series there were 15 rheumatic hearts with minor scarring of the myocardium.

Toxins. Fleischer and Loeb[8] produced experimental myocarditis in 60 per cent of their rabbits with spartein sulphate, caffein and

* It should be recognized, however, that many competent pathologists regard the (perhaps extensive) myocardial scarring of rheumatic cases with normal coronaries as evidence either of a "myocarditis proliferans" or of fibrous replacement of muscle fibers degenerated by the disease process.—EDITOR'S NOTE.

adrenalin injected intravenously, but 5 months later all changes had disappeared except a few small scars. Stewart[9] produced rather extensive scarring of the heart wall with adrenalin injections. None of the cases in the present series gave evidence of having suffered the effects of any known toxin.

Interference With the Blood Supply. Hunter[10] states that arteriosclerosis of the coronary arteries must explain the whole picture of chronic fibrous myocarditis. Brooks[5] found coronary disease in 35 of his 40 syphilitic cases with myocardial changes. He thinks the myocardial degenerations depend upon primary alterations in the coronaries which form a striking feature of the disease. Slater[7] states that in rheumatism the healing of the arteritic and periarteritic foci can cause such sclerotic narrowing of the arterioles that ischemic necrosis may result and that all scars are due either to plugging of the vessels from thrombi or to anemic necrosis from their constriction.

As may be seen from the tabulation of the cases in this series given above, almost all the cases in which there were myocardial scars showed changes in the coronary arteries, although there were also cases of coronary disease without any myocardial scarring.

The rheumatic group shows the least coronary disease and the least myocardial scarring, although in those occasional cases in which there was marked coronary sclerosis there was also a correspondingly extensive scarring. Among the syphilitic cases in general there were some with complete occlusion of the coronary lumen, especially near or at its mouth, others with more extended sclerosis of the coronary and thrombosis. But there were 18 cases of syphilitic aortitis in which there was neither scarring of the heart nor coronary disease. The arteriosclerotic cases which form the great bulk of the whole group, 59 of the 110 cases, show every degree of distortion and narrowing of the coronary arteries, often with calcification and complete occlusion in which terminal thrombosis plays a part.

Gross[11] has made beautiful injections of the coronaries in normal hearts in various decades of life and finds that the older the patient, the better adapted is the heart to receive the brunt of the obliteration, even of a main coronary, not only on account of the development of abundant and free anastomoses, but also from the formation of a dense feltwork of arterial telæ adiposæ. This may perhaps affect the numerical relation of the rheumatic and syphilitic cases to the arteriosclerotic since the latter usually occur in much older people.

Conclusions. In this series of 1000 cases it is not evident that infectious diseases or toxins give rise directly to fibrosis of the myocardium, although they may be concerned in producing arteriosclerosis of the coronary arteries.

Direct invasion of the heart muscle in syphilis and rheumatism plays a minor rôle in the pathogenesis of myocardial scarring.

Disease of the coronary arteries, which was present in 70 of the 110 cases, causing either infarction or more slowly produced ischemic necrosis of the muscle fibers, is advanced as the important etiologic agent of myocardial scarring ("chronic fibrous myocarditis").

NOTE.—I am indebted to Dr. W. G. MacCallum for his assistance in examination of the material and advice in preparation of the paper.

BIBLIOGRAPHY.

1. O'Hare, J. B., Calhoun, A. W., and Altnow, H. O.: Etiology of Chronic Myocarditis, J. Am. Med. Assn., 1928, **90**, 1436.
2. Fahr, G.: Etiology of the Chronic Heart Muscle Diseases of Frequent Occurrence in General Practice, Minnesota Med., 1926, **9**, 5.
3. Brooks, H.: Degenerative Diseases of the Heart Muscle: Its Cause, Types and Diagnosis, Am. Pract., 1913, **47**, 395.
4. Warthin, A. S.: The Persistence of Active Lesions and Spirochetes in the Tissues of Clinically Inactive or "Cured" Syphilis, Trans. Assn. Am. Phys., 1914, **29**, 416.
5. Brooks, H.: A Study of the Heart in Syphilis, Med. Rec., 1912, **81**, 351.
6. MacCallum, W. G.: Textbook of Pathology, 3d ed., Philadelphia, W. B. Saunders Company, 1924, p. 571.
7. Slater, S.: Involvement of the Coronary Arteries in Rheumatic Fever, AM. J. MED. SCI., 1930, **179**, 22.
8. Fleischer, M. S., and Loeb, L.: Experimental Myocarditis, Arch. Int. Med., 1909, **3**, 78; Further Investigations in Experimental Myocarditis, Arch. Int. Med., 1910, **6**, 427.
9. Stewart, H. A.: The Mode of Action of Adrenalin in the Production of Cardiac Hypertrophy, J. Path. and Bact., 1912, **17**, 64.
10. Hunter, O. B.: The Pathologic Elements Underlying Myocardial Degeneration, Cardiac Failure and Cardiac Rupture Resulting from Acute and Chronic Occlusion of the Coronary Vessels, Kober Foundation Address before the Medical Society of District of Columbia, March 27, 1926.
11. Gross, L.: The Blood Supply of the Heart, New York, P. B. Hoeber, Inc., 1921.

GALL BLADDER INFECTION AND ARTHRITIS.

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THE gall bladder is frequently mentioned as a focus of infection in discussions of chronic rheumatic disease, especially in the arthritids. There is, however, a paucity of thorough, clinical studies on the subject. In order to determine the frequency and importance of gall bladder infection in chronic rheumatic disease, this study of 200 cases was undertaken.

The general principle of focal infection in its relationship to arthritis will receive no detailed attention here. It will suffice to state that we are aware of the variety of opinions on this subject.

Some workers, particularly in European centers, deny any direct relationship between focal infection and the arthritides. Others[1] feel that the widespread systemic disturbances we call rheumatic are the result of an actual bacteremia arising in a distant focus and resulting in a deposition of organisms in the affected joints, still others[2] that the systemic changes are the result of a general "hyperergic," or allergic state, the blood and joints remaining sterile. While there is a difference of opinion as to the mechanism by which a focus causes arthritis, there is in the literature an almost universal agreement on the principle of focal infection as the etiologic agent in rheumatic disease.

Poynton and Paine[3] in England, Miller in Berlin, Billings in the United States, to mention a few of the workers upon whom we lean, have made extensive bacteriologic contributions to the subject of focal infection and its importance in chronic rheumatic disease. As a result of these studies, particularly in the past 10 years, the relative importance of certain foci has been emphasized. Thus Pemberton and Pierce,[4] in one series of rheumatic cases, mention the occurrence of dental infection in 54 per cent, nose and throat and accessory sinuses in 31 per cent of the cases. Willcox[5] found dental sepsis in 72 per cent; tonsillar in 10 per cent. Cecil and Archer[6] found dental sepsis in 33 per cent and tonsillar in 61 per cent of their series. The incidence of gall bladder disease as a focus receives only occasional mention in a few reports. What definite part does it play, if any? Is gall bladder infection worthy of consideration as a possible etiologic agent in arthritis?

Deaver[7] makes the statement in a passing reference, that occasionally rheumatoid arthritis may be traced directly to an infected gall bladder. Pemberton,[8] in a study of 33 cases for gall bladder foci, after remarking on the unsatisfactory status of diagnosis of gall bladder disease along medical lines, reports the results of duodenal drainage and culture. There is no record of the number of cases of arthritis from which this series was drawn, or of the result of cholecystography.

Methods of Determining Gall Bladder Infection. In the diagnosis of gall bladder infection we have been guided by four methods of approach: (1) History, (2) Roentgen rays, (3) duodenal drainage and (4) blood chemical findings. It is not our purpose to evaluate various methods of gall bladder diagnosis. There is still contention revolving about each one of these criteria. The clinical history is considered by many to be as diagnostic as any other approach. We use this as our starting point, all patients complaining of even the mildest gall bladder symptomatology receiving further investigation.

Whether or not gall bladder disease means gall bladder infection is still in dispute. The generally accepted opinion and the bulk of evidence tends to show that the disorders are microbic in origin.

Pathologic gall bladders, therefore, as determined by Roentgen rays, are considered infected gall bladders. Cholecystography by the Graham method is now considered extremely accurate in diagnosing gall bladder disease. Thus, Graham[9] (1926) found the method to be correct in 97.2 per cent of the cases verified at operation, Case[10] (1929) claims 90 per cent accuracy, Graham[11] (1931) 100 per cent, Feldman[12] (1930) 94.3 per cent, Beilin and Carlson[13] (1931) 98.3 per cent, the error in diagnosis being 1.7 per cent. Writers vary somewhat in their claims for accuracy from 78 to 100 per cent. About cases that are declared negative by cholecystography and do not come to operation we, of course, know nothing. We, ourselves, used oral administration of the dye. Intravenous administration is considered somewhat more accurate. The conclusion is that, while cholecystography does not always give evidence of stone, it is a very accurate indicator of gall bladder infection.

Duodenal drainage is of interest because of the possible bacteriologic and microscopic constituents of the bile obtained. Bacteriologically the information obtained is often questionable. In the first place the technique of sterile duodenal drainage is extremely difficult and by some is claimed to be impossible. In the second place, streptococci are often found in the normal duodenum. Third, bacteriology of the bile gives absolutely no indication of infection of the gall bladder wall. Judd, Mentzer and Parkhill,[14] in 193 cases of diseased gall bladders removed at operation from which bile was aspirated, found positive cultures in only 14 per cent compared with 98 per cent of positive cultures when made from the wall of the gall bladder. Wilkie[15] found the bile was sterile in the vast majority of cases of chronic cholecystitis, while Alvarez, Meyer *et al.*[16] obtained positive cultures from 82 per cent of the calculous and from 57 per cent of the noncalculous gall bladder walls. The reasons for this are not quite clear, but it is suggested that the bile, especially if concentrated, is bactericidal. Certainly duodenal drainage gives no real indication of gall bladder tissue infection. Only positive findings can have a value, negative results being no index of the status of the gall bladder wall. The findings of Bacillus coli in the duodenum after a fast is considered indicative of infection. Microscopic findings in the bile are also in dispute. The origin of B bile has not yet been conclusively proved. Opinions run from those of Sweet[17] and Halpert[18] who question whether or not bile ever passes out of the gall bladder through the cystic duct, to those who claim that some gall bladder bile is obtained through the duodenal tube and that the method gives additional information, often showing trouble where gall bladders are negative to Roentgen ray. The findings considered important are cholesterol crystals, calcium and bilirubinate pigment which are indications of stone, and bile-stained pus, mucus and epithelial cells, which indicate infection. A confusing factor is that leukocytes and epithelial cells

are commonly found in the duodenum of normal patients. Emphasis is placed on whether or not these constituents are bile stained.

The blood chemistry has doubtful value. There is very little known on the relation of blood chemical findings to cholecystitis. A high cholesterol (above 200) may mean stone. The cholesterol esters usually parallel the cholesterol. Blood urea is frequently low in diseases of the bile ducts and liver.

Method. In 200 consecutive cases of chronic rheumatic disease of all types (rheumatoid arthritis, osteoarthritis, myositis and neuritis) every patient who by history and physical findings was suspected of gall bladder disease received special investigation. Of the 200 patients, 30 fell in this group. All 30 were subjected to cholecystography, using the oral administration of dye. Where any doubt arose, additional evidence was sought in duodenal drainage and blood chemistry. Dr. R. F. Carter and Dr. R. Twiss kindly coöperated with us in this phase of the work.

Findings. Twenty-five of this group of 30 patients were found to have normal gall bladder function according to cholecystography, while 5 were considered infected. Of these 25 negative cases, 13 received additional investigation by way of the duodenal tube and blood chemistry. Four of these patients, in spite of negative Roentgen-ray findings, gave positive evidence of infection by duodenal drainage. Of these 4, 3 revealed streptococci and cholesterol crystals in drainage while 1 repeatedly showed evidence of Bacillus coli infection. The evidence, weak as it might be in some respects, was substantiated in every case by definite clinical evidences of cholecystitis.

RHEUMATIC PATIENTS IN WHOM A DIAGNOSIS OF CHOLECYSTITIS WAS MADE.

Case No.	Cholecystography.	Duodenal, microscopic.	Drainage, bacteriologic.	Blood chemistry.	
				Urea.	Cholesterol.
73611	Pathologic	Bile pigment; calcium; cholesterol	Nonhemolytic strep.	4.7	0.217
66403	Pathologic	Bile pigment; calcium cholesterol; bile stained w.b.c.	Staph. alb.	..	0.244
44719	Pathologic	Calcium; cholesterol	Staph. alb.	8.9	0.185
66091	Pathologic	.....	.....	9.7	0.194
30948	Pathologic				
48912	Negative	Calcium; bile stained w.b.c.; bile pigment	Nonhemolytic strep. Staph. alb.	7.2	0.256
81313	Negative	Cholesterol	Nonhemolytic strep.	13.1	0.175
48410	Negative	Bilirubinate pigment calcium; cholesterol	Nonhemolytic strep. Staph. alb.	5.3	0.300
29281*	Negative	.....	B. coli (2 drainages)	13.0	

* The history and physical examination in all cases supported the diagnosis of cholecystitis.

The diagnosis of the 5 found positive on cholecystography was supplemented in part by evidence from duodenal drainage. A table showing the pertinent facts in each positive case is appended. It will be seen that 9 (4.5 per cent) proved to have gall bladder disease.

Of these 9 patients, 6 had the osteoarthritic type of arthritis, whereas 3 had the type commonly considered infectious. As usual the former fell within the older age group (40 to 60 years). The average age of all 9 was 44 years. All were females. One of these 9 was subjected to cholecystectomy and was given a vaccine made from the organisms found in the duodenum. Others received repeated therapeutic drainage. In no case did these measures materially help the arthritis.

Comment. In 200 patients with chronic rheumatic disease, only 4.5 per cent gave any evidence whatever of gall bladder infection. It is of interest to compare this figure with the much higher incidence of nasal, pharyngeal and dental infection in arthritis. To compare it with the incidence of gall bladder disease in general is of even more importance. At the Mayo Clinic, in 49,659 general admissions the incidence of gall bladder disease was 5 per cent.[19]

The fact that all our positive cases were females is also of significance, the usual sex distribution in cholecystitis being 2 females to 1 male. Also the average age (44 years) is to be noted, and the fact that most of them have passed their menopause, since gall bladder disease ordinarily occurs in both of these groups.

Conclusion. Our study reveals that, in 200 cases of various chronic rheumatic conditions, the incidence of gall bladder infection is no higher than in any group of general hospital admissions. In no case was cholecystitis seen to be a definite factor in etiology.

BIBLIOGRAPHY.

1. Cecil, R. L., Nicholls, E. E., and Stainsby, W. J.: Etiology of Rheumatoid Arthritis, Am. J. Med. Sci., 1931, **181**, 12.

2. Swift, H. F.: Rheumatic Fever, Hektoen Lecture, Billings Foundation, J. Am. Med. Assn., 1929, **92**, 2071.

3. Poynton, F. J., and Paine, A.: The Etiology of Rheumatic Fever, Lancet, 1900, **2**, 861 (Fig. 5), 932 (Fig. 4).

4. Pemberton, R., and Pierce, E. G.: Clinical and Statistical Study of Chronic Arthritis Based on 1100 Cases, Am. J. Med. Sci., 1927, **173**, 31.

5. Willcox, Sir W.: The Diseases of the Periodontal Tissues Due to Infection in Their Relation to Toxemia: The Systemic Effects, Brit. Dent. J., 1923, **44**, 537.

6. Cecil, R. L., and Archer, B. H.: Classification and Treatment of Chronic Arthritis, J. Am. Med. Assn., 1926, **87**, 741.

7. Deaver, J. B.: Sequelæ of Biliary Tract Infection, J. Am. Med. Assn., 1930, **95**, 1641.

8. Pemberton, R.: Arthritis and Rheumatoid Conditions, Their Nature and Treatment, Philadelphia, Lea & Febiger, 1929.

9. Graham, E. A.: New Developments in Our Knowledge of Gall Bladder, Am. J. Med. Sci., 1926, **172**, 625.

10. Case, J. T.: Present Status of Roentgenologic Diagnosis of Gall Stones, Canadian Med. Assn. J., 1929, **20**, 380.

11. Graham, E. A.: Prevention of Carcinoma of Gall Bladder, Am. Surg., 1931, **93**, 317.

12. Feldman, M.: Cholecystography: Analysis of 500 Cases Observed by Means of Oral Method, Radiology, 1930, **15**, 675.
13. Beilin, D. S., and Carlson, G. D.: Clinical Value of Cholecystography by the Oral Method, Radiology, 1931, **17**, 559.
14. Judd, E. S., Mentzer, S. H., and Parkhill, E.: Bacteriologic Study of Gall Bladders Removed at Operation, Am. J. Med. Sci., 1927, **173**, 16.
15. Wilkie, A. L.: Bacteriology of Cholecystitis: Clinical and Experimental Study, Brit. J. Surg., 1928, **15**, 450.
16. Alvarez, W. C., and others: Gall Bladder Infections, J. Am. Med. Assn., 1923, **81**, 974.
17. Sweet, J. E.: Gall Bladder: Its Past, Present and Future, Internat. Clin., 1924, **1**, 187.
18. Halpert, B.: Research on Gall Bladder, Med. Klin., 1924, **20**, 408.
19. Mentzer, S. H.: Clinical and Pathologic Study of Cholecystitis and Cholelithiasis, Surg., Gynec. and Obst., 1926, **42**, 782.

CARBARSONE THERAPY IN AMEBIASIS.

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An opportunity was afforded, by a current protozoölogic survey of new admissions to San Quentin Prison, to study the effectiveness of 4-carbaminophenyl arsonic acid (carbarsone)* in amebiasis under excellent conditions of control, in the effort to determine whether or not a previous report on the usefulness of this drug in amebiasis[1] might be confirmed. Judgment as to the effectiveness of the therapy was based on the same criteria which were generally discussed by Reed and his associates.[1]

Forty-two patients have been observed, with careful and frequent stool examinations, for 3 or more months following cessation of treatment. Four other patients were paroled before such an observation period could be completed, and it was impossible to follow them satisfactorily. Two of these 4 had recurrence of stools positive for Entamœba histolytica after the first course of carbarsone therapy (5 gm. in 10 days); one 6 weeks after cessation of treatment and another after 7 weeks. Both these patients had heavy infections. A second course of carbarsone therapy cleared the stools promptly, and they were negative for Entamœba histolytica when the patients were paroled, both 1 month after stopping

* Supplied by Eli Lilly & Co., Indianapolis, Ind.

the second course of treatment. Another patient with a severe infection with liver involvement (No. 37, Table 1) had a recurrence of positive stools after the first course of treatment with carbarsone. This patient received another course of carbarsone, a total of 20 gm. in 7 weeks, after which his stools remained clear for 2 months and then became positive again. He had previously been treated with emetin hydrochlorid and other amebicidal agents.

TABLE 1.—RESPONSE OF PATIENTS INFECTED WITH ENTAMŒBA HISTOLYTICA TO CARBARSONE THERAPY.*

Patient No.	Symptoms and signs.	Observation period *after* treatment in months.	Stools examined after treatment and found negative.	Response.
1	+	6	24	C. P.
2	−	6	23	C.
3	+	6	25	C. P.
4	+	6	23	C.
5	+	7	24	C.
6	+	7	25	C. P.
7	+	6	21	C. P.
8	+	6	22	C. P.
9	+	6	22	C. P.
10	−	6	24	C.
11	+	6	24	C. P.
12	−	5	23	C.
13	+	5	23	C.
14	+	5	24	C. P.
15	+	5	24	C.
16	−	5	21	C.
17	+	5	23	C. P.
18	+	5	24	C. P.
19	+	5	24	C. P.
20	+	5	25	C.
21	+	5	25	C. P.
22	+	4.5	24	C. P.
23	+	4.5	24	C.
24	−	4.5	25	C.
25	−	4.5	21	C.
26	+	4.5	24	C.
27	+	4.5	24	C. P.
28	+	3.5	18	C.
29	−	4	21	C.
30	−	4	21	C.
31	−	4	21	C.
32	+	4	24	C.
33	+	4	24	C.
34	+	5	24	C. P.
35	+	4.5	23	C. P.
36	−	4.5	24	C.
37*	+	1	9	Positive again.
		2	15	Positive again. P.
38	+	3.5	25	C. P.
39	+	3.5	24	C. P.
40	−	4	21	C.
41	−	3	24	C.
42	+	3	21	C. P.

C. = stools cleared. P. = patient improved.

* All patients except No. 37 received 5 gm. carbarsone orally in 10 days; No. 37 received two such courses of treatment in 2 months.

In the ordinary case of chronic amebiasis with relatively mild symptoms, we have found that a total of 5 gm. of carbarsone, administered orally at the rate of 0.25 gm., twice daily for 10 days, is sufficient to clear the stools and to bring about clinical improvement. In severe infections this course of treatment may have to be repeated and in severe diarrhea it should be supplemented with carbarsone retention enemata (2 gm. carbarsone in 100 cc. of 1 per cent sodium bicarbonate solution), in order to achieve a satisfactory result.

No symptoms of arsenic toxicity were noted in any of these patients. Five patients, who received carbarsone purified by a different method from that employed in other lots of the drug which we used, gave evidence of local gastric irritation. This disappeared promptly, and was not observed subsequently on continuing treatment with carbarsone purified by the original method.

Conclusions. Our findings generally confirm those reported by Reed.[1] All but 1 of a group of 42 cases of amebiasis observed for 3 or more months after oral treatment with carbarsone were successfully cleared of Entamœba histolytica (as far as careful stool examinations could reveal), without toxic effect and without hospitalization. It is our opinion that carbarsone offers a relatively nontoxic, satisfactory and cheap means of inaugurating therapy in amebiasis. It seems to be quite as effective as emetin, and is to be preferred as an initial therapeutic agent, because of the definite evidence of pathologic damage from emetin in the doses necessary for clinical effectiveness.[2] Acetarsone and chiniofon do not show as satisfactory an effect in amebiasis as we have found for carbarsone. In severe cases of amebiasis the recommended dosage of carbarsone (5 gm. in 10 days) may not be enough. Repetition of the course of therapy, supplemented with carbarsone retention enemata, is then indicated. Only after this would one seem to be justified in incurring the risks involved in emetin therapy.

BIBLIOGRAPHY.

1. Reed, A. C., Anderson, H. H., David, N. A., and Leake, C. D.: J. Am. Med. Assn., 1932, **98**, 189.

2. Anderson, H. H., and Leake, C. D.: Am. J. Trop. Med., 1930, **10**, 249. Rinehart, J. F., and Anderson, H. H.: Arch. Path., 1931, **11**, 546

REVIEWS.

A Textbook of Human Physiology. By August Krogh, Ph.D., LL.D., Professor of Zoöphysiology in Copenhagen University, Copenhagen. Revised and edited by Katherine R. Drinker, A.B., M.D., formerly Research Assistant in Applied Physiology, Harvard Medical School, Boston. Pp. 233; 108 illustrations. Philadelphia: Lea & Febiger, 1932. Price, $2.75.

This English translation of the author's book should prove a useful presentation of the elements of physiology. The facts are presented with a simple clarity worthy of a great master. Dr. Katherine Drinker in translating it has also added many useful, clear diagrams. The sections on circulation and respiration and the ideas of quantitative anatomy therein introduced make these sections particularly outstanding. Throughout the book there are few inaccuracies, though perhaps the treatment of the nervous system is the weakest part.

The Danish edition was prepared for school children of 16 to 18 years of age and for such students the book appears ideal. The English edition has been designed for the use of college students and one can only comment that if this is the kind of study that the college students carry on in American universities, it is a serious reflection on the standards of the colleges and confirms the criticisms that American colleges carry on too much superficial and elementary teaching. H. B.

The History of Medicine. By Bernard Dawson, M.D. (Lond.), F.R.C.S. (Eng.). Pp. 160; 31 illustrations. London: H. K. Lewis & Co., Ltd., 1931. Price, 7s. 6d.

An evaluation of a volume that covers such a large field in such a short space is scarcely less difficult than its original composition. In order to avoid a mere cataloguing of facts certain items must necessarily be given more than their proper space, while others which may happen to appeal to the reviewer more than to the writer are properly entirely omitted. Perhaps the fact that these 7 lectures have proven profitable and entertaining for the junior medical students for whom they were prepared is sufficient guarantee of the value of the work to others. With such thoughts in mind, however, we question the value of such a book as compared to others of twice the cost and three times the size, that have mostly original instead of borrowed illustrations. All the more need too for a bibliography to help those who wish to read further in the matter. E. K.

Allergy and Applied Immunology. A Handbook for Physician and Patient, on Asthma, Hay Fever, Urticaria, Eczema, Migraine and Kindred Manifestations of Allergy. By Warren T. Vaughan, M.D. Pp. 359; 21 illustrations and numerous tables. St. Louis: The C. V. Mosby Company, 1931. Price, $4.50.

There are few conditions in which the *intelligent* coöperation of the patient is so essential for successful treatment as in the manifestations of

allergy. Physicians working in this field will therefore welcome this book for the better training of their patients. The general practitioner, also, will find an adequate statement of our present practical knowledge of allergy, as well as numerous references as a guide to further reading. The author brings to his task not only a thorough mastery of his subject, but also a delightfully clear and vivid literary style. R. K.

PAYING YOUR SICKNESS BILLS. By MICHAEL M. DAVIS. Pp. 276. Chicago: University of Chicago Press, 1931. Price, $2.50.

AN interesting analysis of a complicated problem: the unevenness of the burden of sickness as it affects individuals, the factors which enter into the increasing costs of medical care, the attempts which have thus far been made to solve the problem. The author concludes that the solution lies fundamentally in the distribution of the financial burden either by taxation or by insurance. Physicians and laymen will find here not only food for thought but a guide for action. R. K.

CLINICAL ALLERGY. ASTHMA AND HAY FEVER. By FRANCIS M. RACKEMANN, M.D., Physician to the Massachusetts General Hospital; Instructor in Medicine, Harvard Medical School. Pp. 617; 29 illustrations. New York: The Macmillan Company, 1931.

THE author states that the objects of this book are to digest the enormous mass of literature that has accumulated on this subject and by means of these sources, and particularly from personal experience, to define the present-day conception of the mechanism of asthma, hay fever and allied disorders and to discuss methods of diagnosis and treatment. He has succeeded admirably in producing a book which the general practitioner and the student will find complete, authoritative and readable. Special workers in the field will appreciate the extensive bibliography. R. K.

GYNECOLOGIC ROENTGENOLOGY. By JULIUS JARCHO, M.D., F.A.C.S., Attending Gynecologist and Obstetrician, Sydenham Hospital, New York. VOL. 13. ANNALS OF ROENTGENOLOGY. Edited by JAMES T. CASE, M.D., Professor of Roentgenology, Northwestern University Medical College, Chicago. Pp. 571; 273 illustrations, 5 colored plates. New York: Paul B. Hoeber, Inc., 1931. Price, $20.00.

IN this monograph the author discusses the roentgenologic methods of diagnosis with the aid of pneumoperitoneum and iodized oil injections of the uterus and tubes. Ordinary roentgenology has little use in gynecology, being limited, according to the author, to the diagnosis of calcified fibroids, in which condition roentgenologic therapy is contraindicated.

The author discusses at length both pneumoperitoneum and uterosalpingography. The technique of both methods is detailed, not only as to the induction, which is of value to the gynecologist, but, as well, the roentgenologic details as to position, exposure and interpretation of the resulting picture. The author's experience with uterosalpingography has evidently been extensive. To emphasize certain points in technique and diagnosis he has introduced many pertinent case histories. A short section on radiation therapy gives in a concise, clear manner the major

points in generally accepted present-day technique. The book is profusely illustrated with excellent reproductions of appropriate roentgenograms and a number of color plates. It is in every sense an atlas of the subject. The literature has been widely searched and liberally quoted, and a large bibliography is appended, following which is an authors' name index.

While the author suggests that the volume is intended as a guide for roentgenologists assisting in such diagnostic methods, it should also be of unusual value to gynecologists as a very full exposition of the value of roentgenology in gynecologic diagnosis and therapy.

P. W.

APPROVED LABORATORY TECHNIQUE. Prepared under the Auspices of The American Society of Clinical Pathologists. By JOHN A. KOLMER, M.D., Dr.P.H., D.Sc., LL.D., Professor of Pathology and Bacteriology, Graduate School of Medicine, University of Pennsylvania, and FRED BOERNER, V.M.D., Associate Professor of Bacteriology, Graduate School of Medicine, University of Pennsylvania, Assisted by C. ZENT GARBER, A.B., M.D., Associate in Pathology, Peking Union Medical College, and Committees of The American Society of Clinical Pathologists. Pp. 663; 300 illustrations, 11 plates. New York: D. Appleton & Co., 1931. Price, $7.50.

EVEN with the great number of books on laboratory technique that have recently flooded the market, this one should be welcomed not only on account of its intrinsic merits but on account of the official sanction that it received from The American Society of Clinical Pathologists. With the many and continuing additions to laboratory methods useful in clinical medicine, it has been inevitable both that the standards of technical performance should suffer and that the clinician often should not have sufficient knowledge to make maximum use of laboratory helps. Emphasis on the indispensability of accurate and reliable apparatus and reagents, and inclusion of methods used by practising veterinarians are noteworthy items in this book. It is richly and intelligently illustrated; however, the colors, especially of erythrocytes, are disappointing. Many would not agree that the exact source of platelets is as yet unknown (p. 95); "Reticulated erythrocytes" (pp. 92 and 93) is an obsolete term. Terry's quick surface staining biopsy method is not found. A more serious criticism is the omission of original references, which greatly restricts the potential value of this otherwise excellent book.

E. K.

THE MONGOL IN OUR MIDST. By F. G. CROOKSHANK, M.D., F.R.C.P. Pp. 539; illustrated. Third edition greatly enlarged and entirely rewritten. London: Kegan Paul, Trench Trubner & Co., Ltd., 1931. Price, 21s. net.

DOUBTLESS many will remember a small volume of the Today and Tomorrow series that caused amusement several years ago by the comparison of 3 main human stocks, Caucasian, Mongol and Negro, to the chimpanzee, orang-utang and gorilla. This has now reappeared, much enlarged and more fully documented, in a form that enables the author to put forward adequately the ideas that he has held for many years. Whether or not readers are convinced by his argument—and I doubt if many will be

—they at least will recognize the sincerity of the author and a measure of skill in maintaining a difficult thesis.

That the occurrence of Mongoloids in Caucasian populations is of anthropological as well as medical importance is a statement that will doubtless find considerable support. That the similarities which the author elicits among Mongols, mongoloids and orangs show a common ancestral origin for the three, closer for instance than Mongols and Caucasians, is a far different matter. The assumed relationship of negros to gorillas and to Langdon-Down's Ethiopian idiot and of whites to chimpanzees and to microcephalics likewise remains unconvincing in spite of suggestive similarities of appearance and geographical distribution. The chimpanzee and the Sheikh of Fig. 9 seem remarkable for their dissimilarity; but one wonders why certain Irish types were not utilized.

Though the literary style adopted is better suited to entertain than to convince, the more serious minded reader will find plenty of pabulum set forth in the Appendices and extensive Bibliography. E. K.

MEDICAL MEN IN THE AMERICAN REVOLUTION, 1775–1783. The Army Medical Bulletin, No. 25. By LOUIS C. DUNCAN, LIEUT.-COLONEL, U. S. Army, Retired. Pp. 414; 53 illustrations. Carlisle Barracks, Pa.: Medical Field Service School, 1931.

FOR the interesting and important medical history of the Revolution, one has hitherto had to turn to James Thatcher's Journal, Surgeon-General Tilton's book on military hospitals, or such necessarily brief chapters as in Packard's "Medical History of the United States," or *ex parte* essays, such as John Morgan's "Vindication." Colonel Duncan's scholarly work not only remedies this deficiency but has combined with an authoritative statement a delightful story that once begun is apt to be read from cover to cover. Though the 52 illustrations are listed, by a curious oversight there are neither Index nor Table of Contents to the book. As the reviewer had to make his own Table he is passing it on the reader: Chapter 1, Medicine and Surgery in the Colonies; Chapter 2, Making of the Army; Chapter 3, Siege of Boston; Chapter 4, The Canada Expedition; Chapter 5, The New York Campaign of 1776; Chapter 6, New Jersey Campaign; Chapter 7, Reorganization of the Army; Chapter 8, The Campaign for Philadelphia; Chapter 9, Burgoyne's Campaign; Chapter 10, 1778—Monmouth; Chapter 11, Medical Director Shippen; Chapter 12, The War in the South; Chapter 13, Medical Director John Cochran; Chapter 14, Yorktown; Chapter 15, The End; Appendix A, Losses; Appendix B, List of Medical Men who Took Part in the Revolution. If this sterling book is adequately known and appreciated, applications for copies to the Medical Field Service School at Carlisle should quickly exhaust the edition of 5000. If so, let us hope that a new edition with these omissions rectified will be made available.

E. K.

THE HARVEY LECTURES, 1930–1931, SERIES 26. Pp. 186; illustrated. Baltimore: The Williams & Wilkins Company, 1931. Price, $4.00.

THE contents of this volume are of interest not only in maintaining the high standard of presentation set by previous volumes but also as exhibiting both the changes in point of view as to well-known conditions and the emergence, often so gradual as to be almost unnoticeable, of new problems of medical importance. The 8 lectures in this volume are: The Female Sex Hormone, by R. T. Frank; Mass Action in Cerebral Function by K. S.

Lashley; Sinanthropus—Peking Man: Its Discovery and Significance by G. Elliot Smith; Psychoanalysis and Medicine by Franz Alexander; Possible Immunologic Reactions in Plants by E. M. East; The Coronary Artery in Health and Disease by James B. Herrick; Cold as an Agent in Physiologic Analysis by Sir William Hardy; Tissue Resistance and Immunity by Frederick P. Gay. While each reader will have his own preferences and the difficulties of condensing large topics into small space are recognized, the Reviewer would especially recommend the lectures of Elliot Smith, Herrick and Hardy. E. K.

THE WHITE HOUSE CONFERENCE PUBLICATIONS ON CHILD HEALTH AND PROTECTION. New York: The Century Company, 1932. *I. Health Protection for the Preschool Child.* By GEORGE TRUMAN PALMER, DR. P.H., Chairman, Subcommittee on Statistics, MAHEW DERRYBERRY, Research Assistant, and PHILIP VAN INGEN, M.D., Chairman, Committee on Medical Care for Children. Pp. 275; 50 charts and numerous tables. 1931. Price, $2.50. *II. Body Mechanics: Education and Mechanics.* Report of the Subcommittee on Orthopedics and Body Mechanics. By ROBERT B. OSGOOD, M.D., Chairman. Pp. 166; illustrated. Price, $1.50. *III. Psychology and Psychiatry in Pediatrics: The Problem.* Report of the Subcommittee on Psychology and Psychiatry. By BRONSON CROTHERS, M.D., Chairman. Pp. 146. Price, $1.50.

I. "This report undertakes to answer the question: To what extent is the health of the children in the United States who are the nucleus of the next generation being protected? The report is based on house-to-house inquiries made by representatives of nearly 1000 different local organizations, reaching 146,000 children in three-fourths of all cities of over 50,000 population and 37,000 children living in the rural areas of 42 states. The result is the most complete and graphic picture of how preventive medical and dental services are being applied to the preschool child which has yet been presented. The book is an invaluable addition to the literature of the preschool child. It includes an introductory statement regarding the present status of preventive medical and dental measures, a discussion of the findings of the survey, a series of reference tables showing in detail the survey findings in each area studied, and a discussion and explanation of the administration of the survey and the computation of the data collected."

II. "Body mechanics is defined . . . as 'the mechanical correlation of the various systems of the body with special reference to the skeletal, muscular and visceral systems.' There is positive evidence to prove that not less than two-thirds of the young children of the United States exhibit faulty body mechanics, and that this condition is likely to continue into adult life. The evidence gathered shows that improvement in body mechanics is associated with improvement in health and efficiency. An important distinction is made in the report between training in the principles of good body mechanics and training in various physical exercises."

III. "This report considers the important question, Should the medical practitioner attempt to give advice when difficulties threaten the satisfactory development of personality in a child under his care? Although the report does not urge all doctors to attempt to become expert in the fields of psychology and psychiatry, it states the opinion that adequate physical care of the child cannot be given without attention to whatever intellectual and emotional difficulties may be present, and concludes that when trouble arises and the individual child is in distress a well-informed and alert physician is the obvious adviser."

TRAITEMENT DE LA TUBERCULOSE PAR LA SANOCRYSIN. By KNUD SECHER, Médécin-Chef à l'Hôpital de Bispebjerg, Copenhague. Pp. 110; 21 illustrations. Copenhagen: Levin and Munksgaard, 1932.

SANOCRYSIN is one of a number of gold preparations employed in therapy of tuberculosis. The first part of the book briefly discusses the chemotherapeutic action of gold in experimentally produced tuberculosis as studied notably by Möllgaard. Different chapters discuss the following aspects: The method of administration and observation of patient; untoward reactions; indications and contraindications; use of gold in different forms of tuberculosis, especially pulmonary tuberculosis; a table of dosage and analysis of results. Excellent results are reported in therapy of medical tuberculosis. The book is a good brief presentation of the status of gold therapy. A number of references are given. Doses above 150 mg. of gold as advocated by the author are now no longer employed in many clinics on account of severe reactions. J. K.

A TEXTBOOK OF MEDICINE FOR NURSES. By E. NOBLE CHAMBERLAIN, M.D., M.Sc., M.R.C.P., Senior Assistant Physician and Cardiologist, Royal Southern Hospital, Liverpool, etc. With a Foreword by MISS E. M. MUSSON, C.B.E., R.R.C., Chairman, General Nursing Council for England and Wales. Pp. 439; 38 illustrations. New York: Oxford University Press, 1931.

IT is the author's object to give nurses a book that will be as practically helpful as possible, one that she may refer to as she cares for the patient and so add constantly to her fund of scientific knowledge.

In a clear, compact manner this text describes most of the problems in medical nursing, that a nurse needs to enable her to give the intelligent and satisfactory care, that is such a welcome help to the physician and comfort to the patient.

The chapters on Bacteriology and Therapeutics include only the essential elements that relate directly to nursing practice.

Special emphasis is given to the medical treatment and nursing care of all diseases discussed. An Appendix describes clearly the common technical procedures used. A Glossary, an Index and a Summary complete the book.

No review could adequately describe the wealth of material, the valuable illustrations and diagrams, some of which are colored, that are found in this book, nor give any hint of the beautiful style in which it is written. Aside from its value as a textbook that could be used with satisfaction anywhere this book is a fine piece of literature.

M. S.

BLOOD SUGAR IN NORMAL AND SICK CHILDREN. By ELISABETH SVENSGAARD. Pp. 245; illustrated. Copenhagen: Levin & Munksgaard, 1931.

IN this monograph, translated into English from Danish, the author eviews the literature and gives her own data on fasting blood sugar values, blood sugar curves after ingested glucose and the effect of repeated glucose tests in the same individual. Data are given on 11 normal newborn infants, 26 normal infants from 15 days to 1 year, 22 normal children from 1 to 13 years of age, 5 children with celiac disease, 5 with chronic dyspepsia, 4 cretins, 5 children with eczema, 5 with rickets and 6 with tetany.

Findings of especial interest were the wide physiologic fluctuations in blood sugar curves after ingestion of glucose in infants on different days, and the very slight rise in the blood sugar after glucose feeding in celiac disease.

Noteworthy features of the work are the completeness of the protocols, and the large number of blood sugar samples taken in each curve.

I. Z.

THE BLACK DEATH AND MEN OF LEARNING. By ANNA MONTGOMERY CAMPBELL, Assistant Professor of History, New Jersey College for Women. Pp. 210. New York: Columbia University Press, 1931.

THIS is the first book of a series to be published under the auspices of the History of Science with the aid of an appropriation of the Carnegie Corporation to "assist in publishing important contributions to knowledge." Dealing with the greatest catastrophe that has befallen mankind in historic times, it tells a tale that is not only of absorbing interest to those who like to consider the present in the light of the past, but is also of scholarly value concerning the effect of the black death on the intellectual classes, the universities and science in general. The plague tractates, so productively studied by Sudhoff, with their revelation of contemporary views on the cause and nature of the disease and the accepted methods of protection, prevention and treatment, are first outlined. Later chapters portray in a well-documented but readable fashion the damage done by the pestilence to medicine, law, theology, politics and the sciences, both in the university and in extracollegiate activities. A 14-page bibliography, in addition to the copious footnotes, paves a broad approach for those who wish to go further.

E. K.

MEMORIE E COMMUNICAZIONI SCIENTIFICHE (1894–1930). By PROF. CESARE SERONO, Dottore in Medicina ed in Chimica, Docente di Chimica e Microscopia Clinica nella R. Università di Roma. Pp. 701. Rome: Instituto Nazionale Medico Farmacologico Serono, 1931.

THE book is a collection of scientific investigations previously published in various journals. The collection represents 40 years of the author's scientific activity and was published on the occasion of the twenty-fifth anniversary of the foundation of his institute.

The articles deal mostly with biologic chemistry, more and more leaning to the field of therapeutics.

Notable among these are studies on cholesterol and lecithin first introduced in human therapy by the author in 1897; studies on the physiologic and therapeutic action of lipoids, with special reference to cholesterol and lecithin (1911); researches on the various digestive ferments, their physiology and preparation in liquid form; studies on the therapeutic action of magnesium and calcium and their synergetic action, and finally (1923) researches on the action and preparation of insulin.

There are also several articles of interest to the clinical pathologist concerning mostly quantitative urinalysis.

The collection is preceded by a brief autobiographic sketch, and closes with a stimulating and somewhat prophetic article on life and radiation.

M. S.

MEDICINE IN VIRGINIA IN THE EIGHTEENTH CENTURY. By WYNDHAM B. BLANTON. Pp. 449; illustrated. Richmond, Va.: Garrett & Massie, Inc., 1931. Price, $7.50.

To the author's former book, *Virginia Medicine in the Seventeenth Century* (AM. J. MED. SCI., 1930, **180**, 715), is now added this larger work covering a period when the Old Dominion was not only in the heyday of her glory, but was *facile princeps* in intellect, wealth and prominence on this continent. A century which put the colonies well on the road to prosperity and developed a galaxy of brilliant minds relatively unequalled at that period or since was bound to have its interesting medical side. This the author has captured for us both in detail and in spirit. Though quacks were all too common, as indeed they always have been in this gullible land, men of high standards and ability were numerous in the profession and the habit of going abroad for one's education was in full swing. Even those who followed the apprentice system carried it out so thoroughly that much more of the available knowledge of the time was acquired by the intelligent student than is possible today.

The author, well versed in his subject, by correlating Virginia medicine with that of Europe and the other colonies, greatly widens the interest of his work to the reader. In the 18 chapters, not only are medicine, surgery and obstetrics depicted in some detail, but the related subjects of pharmacy, dentistry, nursing and botany receive understanding treatment. Especially interesting is the chapter on Jefferson and William Byrd of Westover, as examples of eighteenth century useful amateur scientists in medicine, while the chapter on Washington's last illness is of peculiar appropriateness at this time. Biographies of physicians in various Virginia towns and counties, while of more restricted interest, add to the value of the book as an historical record. The Historical Committee of the Medical Society of Virginia, of which the author is a member, is to be heartily congratulated on this concrete example of their activities. E. K.

LABORATORY DIAGNOSIS. By EDWIN E. OSGOOD, M.A., M.D., Assistant Professor of Medicine and Biochemistry, Director of Laboratories, University of Oregon, School of Medicine, and HAROLD D. HASKINS, M.D., Professor of Biochemistry, University of Oregon, School of Medicine. Pp. 475; 21 figures and 6 colored plates. Philadelphia: P. Blakiston's Son & Co., Inc., 1931. Price, $5.00.

AN outgrowth of the outline used at the University of Oregon in teaching clinical pathology, this book attempts somewhat more than the usual manual of laboratory diagnosis. The usual description of methods, which occupies the latter half of the book, is preceded by 9 chapters on disorders of the various parts of the body that may best be investigated by laboratory methods. Thus in Chapter V (18 pages on Disorders of the Central Nervous System), the routine résumé in black-face type of essential points in anatomy, physiology and biochemistry is followed by a statement of indications for examination of the cerebrospinal fluid and several pages of interpretations of findings. A discussion of the colloidal gold test is followed by an outline of the systematic laboratory investigation of coma. This mode of treatment unavoidably leads to more or less repetition, which at times is *verbatim* (*cp.* erythrocytic diameters, on pages 192 and 375). Also while it undoubtedly offers in convenient form many considerations not included in the conventional laboratory manual, it is problematic whether many of these should not be left for more complete treatment elsewhere. The book is beautifully prepared and its statements accurate; it gives good value for the price charged. E. K.

INTERNATIONAL STUDIES ON THE RELATION BETWEEN THE PRIVATE AND OFFICIAL PRACTICE OF MEDICINE WITH SPECIAL REFERENCE TO THE PREVENTION OF DISEASE. Conducted for the Milbank Memorial Fund by SIR ARTHUR NEWSHOLME, K.C.B., M.D., F.R.C.P. London: George Allen & Unwin, Ltd. Baltimore: Williams & Wilkins Company, 1931. Vol. I contains The Netherlands, Denmark, Sweden, Norway, Germany and Austria. Pp. 248. Vol. II contains Belgium, France, Italy, Jugo-Slavia, Hungary, Poland, Czecho-Slovakia. Pp. 249. Vol. III contains England and Wales, Scotland and Ireland. Pp. 558. MEDICINE AND THE STATE: THE RELATION BETWEEN THE PRIVATE AND OFFICIAL PRACTICE OF MEDICINE WITH SPECIAL REFERENCE TO PUBLIC HEALTH. With a Foreword by WILLIAM H. WELCH, M.D., LL.D., Pp. 300.

THE reviewer draws freely on Foreword and Preface: One of the major problems in public health administration is that of ascertaining the proper sphere of the private physician in the field of public health. During the past 7 years the Directors of the Milbank Memorial Fund have had occasion to consider this problem very seriously, in connection with the opposition of some members of the medical profession to certain phases of public health work inaugurated by the Fund. Finding few precedents in the United States to guide them, the Directors decided to arrange for an international investigation to throw light on the relationship between the fields of activity of private physicians and of physicians and laymen engaged in public health work. Hitherto most countries have evolved measures only as each pressing need has emerged. The different countries have not learned adequately from each other. To shed light on these questions a survey was conducted for the Fund by Sir Arthur Newsholme, M.D., K.C.B., former chief medical officer of the Local Government Board of England and Wales, and lecturer on public health administration, School of Hygiene and Public Health, Johns Hopkins University. The material gathered is presented in the first three volumes. The author points out that the observations have an additional value in that they were all made by the same individual and are therefore comparable. The specific medical problems which figure chiefly in the report are the methods of medical attendance on the poor, the provision of hospital treatment and consultative facilities for the sick, the medical phase of sickness insurance and the special problems of maternity and child welfare work, of school medical work and of work for the treatment and prevention of tuberculosis and venereal diseases. The fourth and concluding volume, *Medicine and the State*, summarizing the subjects as illustrated in the countries, surveyed, and presenting the author's conclusions and suggestions for action, is particularly recommended to all readers. These volumes constitute a contribution of the first importance in the field of social medicine. R. K.

NURSING IN NERVOUS DISEASES. By JAMES W. MCCONNELL, M.D., Neurologist to the Philadelphia General Hospital; Associate Professor of Neurology, Graduate School of Medicine, University of Pennsylvania. Pp. 153; 24 illustrations. Philadelphia: F. A. Davis Company, 1932. Price, $1.50.

THIS book admirably fulfills its purpose to make "life easier for both the student nurse and the patient suffering from organic nervous disease." The many illustrations are aptly chosen and each chapter ends with a list of pertinent review questions. Throughout, the utmost clarity is shown, but one regrets the narrow confines of the subject matter.

The important subjects discussed are: nervous system, nomenclature,

unconsciousness, apoplexy, epilepsy, diseases of the spinal cord, tabes dorsalis, poliomyelitis, neuritis, paralysis agitans, chorea, neuroses and psychoses.

Other useful subjects would be drunkenness, narcotic poisoning, heat prostration, tube feeding and even artificial respiration. The inclusion of nursing in mental diseases would not be difficult, and, since the same methods are frequently employed, not inappropriate.

As the book stands, it pertains too definitely to nursing in the nervous wards of the Philadelphia General Hospital, whereas, it should be worthy of a much larger field. N. Y.

BOOKS RECEIVED.

NEW BOOKS.

Internal Medicine. By various contributors. Edited by JOHN H. MUSSER, B.S., M.D., F.A.C.P., Professor of Medicine in the Tulane University of Louisiana School of Medicine; Senior Visiting Physician to the Charity Hospital, New Orleans. Pp. 1316; 37 illustrations. Philadelphia: Lea & Febiger, 1932. Price, $10.00.

Functional Disorders of the Large Intestine and Their Treatment. By JACOB BUCKSTEIN, M.D., Instructor in Gastrointestinal Roentgenology, Cornell University Medical College, etc. Pp. 223; 60 illustrations and 40 reproductions of radiographs. New York: Harper & Brothers, 1932. Price, $3.00.

The Failing Heart of Middle Life. By ALBERT S. HYMAN, A.B., M.D., F.A.C.P., Cardiologist, Beth David and Manhattan General Hospitals, etc., and AARON E. PARSONNET, M.D., C.M., F.A.C.P., Attending Physician and Cardiologist, Newark Beth Israel Hospital, etc. With a Preface by DAVID RIESMAN, M.D., Sc.D., F.A.C.P., Professor of Clinical Medicine, University of Pennsylvania School of Medicine. Pp. 538; 166 illustrations, some in colors. Philadelphia: F. A. Davis Company, 1932. Price, $5.00.

The Nature of Human Conflicts. By A. R. LURIA, Professor of Psychology at the Academy of Communistic Education; Research Associate, State Institute of Experimental Psychology, Moscow. Translated from the Russian and Edited by W. HORSLEY GANTT, Phipps Psychiatric Clinic, Johns Hopkins University, etc. With a Foreword by ADOLF MEYER, Professor of Psychiatry, Johns Hopkins University. Pp. 431; 133 figures. New York: Liveright, Inc., 1932. Price, $4.00.

Your Teeth and Their Care. By CARL W. ADAMS, D.D.S., San Bernardino, Calif. Pp. 141; 30 illustrations. St. Louis: The C. V. Mosby Company, 1932. Price, $1.25.

A sound elementary explanation in lay language of the structure of the teeth, their diseases and how they should be met.

Endocrine Medicine. Three Volumes and an Index Volume. By WILLIAM ENGELBACH, M.D., F.A.C.P., B.S., M.S., D.Sc., Member of Staff, St. Louis, City, Jewish, Baptist Sanitarium and Maternity Hospitals. With a Foreword by LEWELLYS F. BARKER, Professor Emeritus of Medicine, The Johns Hopkins University School of Medicine. *Vol. I. General Considerations.* Pp. 460; 139 illustrations and 62 tables. *Vol. II. The Infantile and Juvenile Endocrinopathies.* Pp. 473; 109 illustrations and 25 tables. *Vol. III. The Adolescent and Adult Endocrinopathies.* Pp. 862; 255 illustrations and 26 tables. Springfield, Ill.: Charles C Thomas, 1932. Price, $35.00.

Hospitals and Child Health. A Publication of the White House Conference on Child Health and Protection. Reports of the Subcommittees on Hospitals and Dispensaries, CLIFFORD G. GRULEE, M.D., Chairman; Convalescent Care, ADRIAN V. S. LAMBERT, M.D., Chairman; Medical Social Service, IDA M. CANNON, R.N., Chairman. Pp. 279; illustrated with tables. New York: The Century Company, 1932. Price, $2.50.

Pharmacology of the Medicinal Agents in Common Use. By STANLEY COULTER, PH.D., SC.D. Pp. 254. Indianapolis: Eli Lilly & Co., 1932. Price, 50c.

"Heretofore there has been no comprehensive, small-size work on pharmacology. To meet this need Dr. Stanley Coulter, Dean Emeritus of the Purdue University School of Science, spent over three years in the preparation of a compact treatise on the pharmacology of the drugs now in common use by the medical profession. In this work he had the coöperation of members of the medical and research staffs of the Lilly Laboratories. The subjects are alphabetically arranged. Under each title there is a terse statement of the constituents of the drug, its physiologic action, dosage, and brief mention of its more important therapeutic uses. In no sense is this book intended to supplant the larger standard texts on pharmacology. On the other hand, it is the hope of its author and the publishers that the use of the pocket-size book will so intrigue the student in the subject that he will be led to closer studies of the great authorities on pharmacology."

The Psychological Effects of Menstruation. Nervous and Mental Disease Monograph Series No. 56. By MARY CHADWICK. Pp. 70. New York and Washington: Nervous and Mental Disease Publishing Company, 1932. Price, $2.00.

Laboratory Service and the General Practitioner. By ARNOLD RENSHAW, M.D., B.S. (LOND.), D.P.H. (MANCH. and CAMB.), Director of the Laboratory of Applied Pathology and Preventive Medicine, Manchester, etc. With an Introduction by DAN MCKENZIE, M.D. (GLAS.), F.R.C.S.E. Pp. 267; 8 illustrations. New York: Oxford University Press, 1932. Price, $2.50.

NEW EDITIONS.

Principles of Chemistry. By JOSEPH H. ROE, PH.D., Professor of Chemistry, George Washington University Medical School, etc. Pp. 427; 30 illustrations. Second edition. St. Louis: The C. V. Mosby Company, 1930. Price, $2.50.

A simple statement to meet the requirements of a 45-hour course in chemistry for nurses, with over 150 pages of exercises.

The American Illustrated Medical Dictionary. By W. A. NEWMAN DORLAND, A.M., M.D., F.A.C.S., Lieut.-Colonel, M.R.C., U. S. Army, etc. With the collaboration of E. C. L. MILLER, M.D., Medical College of Virginia. Pp. 1493; 941 illustrations, 279 portraits. Sixteenth edition, revised and enlarged. Philadelphia: W. B. Saunders Company, 1932. Plain, $7.00; Thumb Index, $7.50.

A triumph of intelligent condensation, this new edition includes in a volume of convenient size more than 3000 new words, hundreds of which are "not defined in any other medical dictionary." Without laying any claims as an encyclopedia, it includes literally hundreds of indexed portraits, over a hundred tables, a 50-page therapeutic table, 941 illustrations with 105 in color, and a wealth of short biographic statements.

Bailey's Textbook of Histology. By ADOLPH ELWYN, A.M., Assistant Professor of Neurology, and OLIVER S. STRONG, A.M., PH.D., Professor of Neurology, with collaboration of others. Pp. 746; 529 illustrations. Eighth edition, revised and rewritten. Baltimore: Wm. Wood & Co., 1932. Price, $5.50.

This is an especially valuable edition to own as it completes the changes only partly carried through in the previous edition. A new chapter on the Living Cell has been included and the attempt to correlate with function continued. Omission of the architectonics of the nervous system has necessitated a separate book composed of the "nervous" material of the seventh edition.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Viruses.—RIVERS (*Science*, 1932, **75**, 654) writes that this is an age of extremes. There is a universal desire to express everything in the superlative tense; the largest ships in the world, the fastest automobiles, the smallest microörganisms. The fact that certain organisms are too small to be seen by the microscope lens adds importance and mystery to these objects. In the last few years there has been a very general increase in interest of scientists in these organisms and many unusual, odd and strange statements and conclusions have been made regarding the viruses. There is no reason to believe that all infectious diseases can be caused only by fungi, bacteria, spirochetes and protozoa or that all infectious agents must be viable. Some authors contend that in the virus group are included all infectious diseases whose etiologic agents are not known. This certainly cannot hold true for such disorders as smallpox, vaccinia, rabies and poliomyelitis; in other words, that these diseases are not caused by any known agent merely because such an agent is invisible or unable to be grown. On the contrary, writes the author, the viruses of many diseases are quite familiar to those who know. They can be distinguished from each other and from bacteria. Their presence can be ascertained easier and more readily than certain bacteria. They are recognized by the type of host attacked, by the clinical and pathologic pictures they induce and by the immunologic responses they excite. It is not necessary to see electricity nor to recognize it to control it, nor is it essential to see and grow every infectious agent. It has not been definitely proven, moreover, that an infectious agent must be viable; it is possible indeed that inanimate material may be capable of exciting disease just as it may be capable of exciting agglutination reactions when treated with a variety of proteins. It has not been proven and it seems quite unlikely to consider viruses merely as stages in bacterial life; even the existence of bacterial life cycles is doubtful. Other workers have become convinced that viruses are animate, yet they state that the size of the organisms causing foot-and-mouth disease is 8 to 12 $\mu\mu$.

The author, who of course is speaking only for himself. questions if it is possible "for an aggregate of so few protein molecules to be an organized living creature possessed of metabolic and reproductive powers comparable with those of minute bacteria." There is no reason to believe because viruses are smaller than bacteria that all of them are identical in size and shape, nor that they are of the same nature: "Some may be inanimate transmissible incitants of disease, others may be primitive forms of life unfamiliar to us, still others may be minute living organisms." It may be possible that viruses may be situated near the line that separates inanimate from living organisms. The author, furthermore, questions whether it is of supreme importance to know whether the viruses are living or merely the products of cellular perversion which are able to bring about similar perversion in other cells. The mere fact that it is not possible to see and cultivate the agents responsible for poliomyelitis, smallpox or yellow fever does not mean that it would be easier to handle these diseases from the preventive point of view if they could be observed and grown. The viruses of these diseases have been identified and kept bacteria-free. They can reproduce the disease in experimental animals, and protective serum can be obtained. Vaccination against virus diseases is more successful than in nearly any of the bacterial diseases. It is very doubtful indeed if the cultivation of the viruses on ordinary media would lead to obtaining agents superior to those already known, to combat many of the virus diseases. The chief difficulty in controlling these infections lies in the fact that they are spread usually from the upper respiratory tract. As the author rather facetiously suggests, it is essential to breathe and as yet no one has suggested a method to obtain uninfected air for the human beings living among their fellow men. To wait until viruses are seen and cultivated in a lifeless medium is merely to waste time. These diseases have been studied by methods other than the usual bacteriologic technique and a certain amount of success has attended these efforts.

SURGERY

UNDER THE CHARGE OF

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Torsion of the Omentum.—Morris (*Arch. Surg.*, 1932, **24**, 40) notes that Marchette reported the first case of torsion of the omentum in 1851. Corner and Pinches, in 1905, collected 54 cases. The present study brings the observed cases to a total of 217. The normal environment and anatomic arrangement of the great omentum are such as to favor rotation of this structure about its long axis, while the introduction of certain mechanical conditions and pathologic changes within and adjacent to it supply the immediate exciting causes of such rotation. It is clearly established that omental twists are capable of producing clinical symptoms of acute and chronic character, and that this condition therefore merits some consideration in the diagnosis of abdominal conditions. Variation in the intensity of degree of rotation

determines two basic clinical and anatomic types of torsion: (1) The complete, in which acute progressive symptoms and marked pathologic changes are dependent on complete permanent circulatory obstruction at the site of the twist; (2) the incomplete, which is characterized by vague, chronic recurring symptoms and mild pathologic changes in consequence of incomplete, partial or temporary obstruction, which permits repeated spontaneous restitution before pronounced organic changes develop. Diagnosis presents obvious difficulties as indicated by the fact that a correct pre-operative diagnosis was recorded in only 7.9 per cent of 217 cases. A statistical study of the series, however, emphasizes certain essential clinical manifestations and points of history, the recognition of which should enhance the precision of a pre-operative diagnosis. The deliberate fixation of the free margin of the omentum by suture to an adjacent structure may be the source of future complications, and its accidental inclusion during abdominal closure is to be avoided carefully.

Tumors of the Bile Ducts.—MARSHALL (*Surg., Gynec. and Obstet.*, 1932, **54**, 6) finds that indications are that benign tumors of the bile ducts are extremely rare, that carcinoma is by far the most common neoplasm of the ducts, and that carcinoma of the bile ducts is more common in males than in females. Gall stones were present in 43 per cent of the cases on which this study was previously based. Obstructive jaundice has been found in most cases and may be extreme, fluctuating in severity or intermittent. The presence or absence of pain seems to be of little, if any, diagnostic significance. Typical biliary colic is not uncommon with tumors of the bile ducts unassociated with cholecystitis or cholelithiasis. The specific cause of obstructive jaundice is not easily diagnosed before operation. Positive diagnosis is rarely possible. Obstructive jaundice is usually a surgical problem, regardless of the type of lesion which causes the obstruction. Surgical treatment should have a favorable effect, because significant symptoms bring the patient to the physician early in the course of the disease and the tumor is small, slow growing and late to metastasize. Obstructive jaundice usually kills the patient, before the tumor itself has passed the stage of operability. Operations on tumors of the bile ducts carries a high mortality, because of the tendency to hemorrhage and the technical difficulties of operation on the biliary tract.

Skull Fracture Involving the Frontal Sinus.—GARDJIAN and SHAWAN (*Ann. Surg.*, 1932, **95**, 27) report that incidence of frontal sinus fractures in a series of over 2600 cases of skull fracture is around 5 per cent. The majority of sinus fracture cases are asymptomatic. They should be confined to bed for a period of 8 to 10 days at least. They should not be permitted to blow the nose. Intranasal douches are contraindicated. The patient should be watched for infection in the sinus and suppuration within the cranial cavity. Compound fractures in this situation should be operated on as soon as the condition of the patient permits. The posterior wall of the sinus should be inspected. The great majority of frontal sinus fractures should be left alone. The results with conservative treatment are gratifying. The incidence of meningitis in this series was less than 1 per cent.

Sympathetic Ganglionectomy and Trunk Resection in Arthritis: Indications and Results.—HENDERSON and ADSON (*J. Bone and Joint Surg.*, 1932, **214**, 47) state that it is apparent that there is a group of cases of chronic arthritis in which vasospastic phenomena are seen and are responsible for or aggravate the arthritic symptoms. Sympathetic ganglionectomy and trunk resection offer additional aid in the treatment of these patients, but extreme care should be exercised in the selection of cases. Sympathetic ganglionectomy and trunk resection are indicated for young persons who have vasomotor phenomena such as cold, wet, pale or cyanotic extremities, but whose arteries are patent, elastic and not occluded. The operation is not indicated in advanced cases in which there is marked ankylosis; neither is it indicated when the infectious process is still present. The operation affords the greatest amount of relief in the smaller joints of the extremities, fingers, hands, wrists, toes, feet and ankles. When there is involvement of the larger joints, such as the knees, hips, shoulders and spinal column, little is accomplished either in checking the disease or in ameliorating the symptoms.

The Use of Auscultatory Percussion for the Examination of Fractures.—LIPPMAN (*J. Bone and Joint Surg.*, 1932, **14**, 118) writes that auscultatory percussion applied across fractures of the shaft of the femur, humerus and clavicle may be so interpreted as to indicate the presence of a complete fracture, the relative position of the fragments and, during the postoperative course, the development of bony union. The stethoscope bell and the percussing finger should be applied over bony prominences on either side of the fracture and the sound so elicited compared with that produced by the same procedure on the normal side. Sound alteration constitutes the criterion of the test. Pitch and quality changes result from free vibration of the separate fragments and accordingly signify complete fracture or incomplete union. Appreciable diminution in sound intensity indicates poor conduction and reflects absence of end-to-end contact. The application of the test is simple, rapid and entails no discomfort to the patient. The desired information is immediately obtainable. In the hospital it may be employed equally well with the patient on the orthopedic table, in traction apparatus, in bed or in a plaster cast, and is consequently applicable during, as well as following, reduction.

Prostate Operations: Prostatectomy vs. Resection.—DAVIS (*J. Am. Med. Assn.*, 1932, **97**, 1674) states that early recognition and treatment of infection of the prostate is urged to prevent obstructions. Recognition of early obstructions and their correction by transurethral methods will lessen the number of advanced cases of prostatism. Prostatectomy, previously being the avenue offered, deterred many from seeking relief early before irreparable damage to the urinary tract and other organs had occurred. Resection (a term used for instrumental ablation) reduces the removal of the obstructing prostate to a minor surgical operation with the accuracy of a cystoscopic procedure and permits operation in the minutest detail under direct vision. Resection reduces the hospitalization to several days as compared to several weeks for prostatectomy with its economic considerations. In bars and con-

tractures, for accuracy and ease of operation, resection excels any method previously described. In these conditions there is no excuse for more radical measures. In the large hypertrophies that require one or more sections, with its freedom from mortality and discomfort to the patient, it should be the method of choice, as these conditions can be corrected without resorting to major surgical procedures. In inoperable carcinoma relief by resection is to be recommended over permanent suprapubic drainage.

Obstructions to the Ureter Produced by Aberrant Bloodvessels.—YOUNG (*Surg., Gynec. and Obst.*, 1932, **54**, 27) writes that obstruction at or near the ureteropelvic juncture is not infrequently caused by vessels which run from the great vessels to the lower pole of the kidney. Two cases are reported in which these vessels caused an acute flexure, kinking and obstruction of the ureter, in 1 case bilateral and in the other unilateral. In the bilateral case the less affected kidney was operated upon first, and the aberrant vessels obstructing the ureter were clamped, divided and ligated. This was followed by a distinct postoperative reduction in the kidney function on this side. At the second operation the author carried out a new procedure (aplastic operation) by means of which it was possible not only to resect the very redundant pelvic sac, but also in closing it to draw the ureter away from the veins, so as to completely remove all possibility of obstruction. The result obtained in this case was completely satisfactory. The same procedure was carried out in the second case also with complete success. In the first case drainage of a huge hydronephrotic sac was kept up for over 1 month by means of a retained ureteral catheter passing out through the penile meatus. This resulted in an amazing restoration of this kidney, which was previously functionless, to practically normal function, so that it was possible to save this kidney and to carry out the conservative plastic of the pelvis with excellent results.

THERAPEUTICS

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The Treatment of Malignant Neutropenia With Pentose Nucleotids.—The stimulating effect of nucleic acid or its decomposition products on white blood cell formation has occasionally been reported in the literature. JACKSON, PARKER, RINEHART and TAYLOR (*J. Am. Med. Assn.*, 1931, **97**, 1436) now publish the clinical results of treating 20 cases of profound leukopenia with intramuscular or intravenous injections of unbroken, pentose nucleotids ("nucleotid K 96," Eli Lilly Co.). In cases of acute illness 0.7 gm. of the nucleotid in 100 cc. of saline solu-

tion was injected intravenously, daily for 4 days; 0.7 gm. in 10 cc. of distilled water was also given intramuscularly on the same days and on each subsequent day until improvement was evident. Certain patients showed a sharp, temporary reaction to the intravenous injection. Seven of 13 patients with an apparent agranulocytic angina recovered under this treatment. In another patient the temperature and blood picture became normal but death intervened from pulmonary hemorrhage. Definite signs of clinical improvement appeared on the third or fourth day of the treatment. The blood picture improved between the fourth and seventh days, usually on the fifth. The total and differential blood cell count became normal 10 days after the treatment was started. Symptomatic improvement and healing of the ulcers occurred simultaneously with the improvement in the blood picture. All of 5 cases of malignant neutropenia associated with infection, treated similarly, recovered. In these 5 cases and the 8 with agranulocytic angina the charts of the temperatures and of the blood cell counts were practically identical. There is evidence that the nucleotid acted beneficially also in 2 cases of chronic benzene poisoning observed over a long period of time. In 1 case recovery appears certain. From the recovery of 14 out of 20 cases of malignant neutropenia treated with nucleotids, the authors conclude that these compounds react favorably on the inactive bone marrow of certain cases with this condition. They emphasize, however, that nucleotids are ineffective in leukemia and in sepsis without neutropenia and leukopenia.

Prostigmin, a New Peristaltic Agent.—ROTHSCHILD (*Med. Klin.*, 1932, **28**, 365) reports the results of animal investigations upon the actions of a new synthetic alkaloid closely similar in constitution to physostigmin, which is introduced under the name of prostigmin. He finds that, when studied upon the isolated surviving intestine, prostigmin acts essentially as do physostigmin, pilocarpin and acetylcholin, increasing the muscular contractions of the intestine and raising the muscular tone as well as promoting increased peristalsis. It also effectively antagonizes the actions of atropin, adrenalin and papaverin. From these purely pharmacologic studies, it is apparent that the drug may be expected to be of use therapeutically as a substitute for physostigmin. Clinical studies on prostigmin by KOTTLORS (*Ibid.*, p. 366) show that in doses of 0.5 mg., injected subcutaneously, the drug increases intestinal peristalsis in a most effective manner. It not only increases the degree of intestinal contraction but it promotes the forward propulsion of the intestinal contents, probably more satisfactorily than does either physostigmin or pilocarpin. Doses of 0.5 mg. of prostigmin produce little or no disagreeable side actions, the only constant action observed being a slight slowing of the heart rate. It is effective also in man to overcome the action of atropin upon the intestinal tract. Its actions are well developed within about 15 minutes after its injection. These findings are established both by roentgenologic studies of the large intestine and from clinical observations in about 300 patients in whom prompt and effective emptying of the intestine, both of gas and of fecal contents, were secured. The patients included chiefly postpartum women and patients upon whom laparotomy had been performed. The effectiveness of the drug in promoting evacuation

is much increased if a small enema of from 20 to 50 cc. of glycerin be given. The author regards prostigmin as being preferable to physostigmin because of the absence of side actions and because of its production of increased physiologic motility of the intestine without the tendency to produce excessive contraction and cramps.

The Effect of Insulin on Gastric Secretion.—This problem is of special interest, both because of the frequently reduced or absent hydrochloric acid in the gastric secretion of diabetic patients and because of the use of insulin for the increase of appetite and gain of body weight. LURJE and ELIJIN (*Wien. klin. Wchnschr.*, 1932, **45**, 492) studied the effect of 10 to 20 units of insulin on the gastric secretion in 22 cases in which 35 observations were made. In all of the cases with normal or hyperacidity there was an increase in the gastric acidity due to insulin. In cases with gastric anacidity insulin usually produced no change, but in some instances hydrochloric acid appeared following insulin therapy.

PEDIATRICS

UNDER THE CHARGE OF
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Milk Irradiated by Carbon Arc Lamp.—HESS and LEWIS (*J. Am. Med. Assn.*, 1932, **99**, 647) activated pasteurized milk by means of carbon arc rays, and carefully controlled and measured the radiant energy. They found that exposure of 16 seconds was sufficient to render the milk antirachitic. A clinical test of this product in the prevention and cure of infantile rickets showed that it is a highly effective antirachitic agent which can be relied on. Less than 1 quart daily sufficed to protect even negro infants. The great advantage of using activated milk, both fluid and in the dry form, in the prophylaxis of rickets, is that this furnishes an automatic method of therapy and likewise provides calcium and phosphorus. Laboratory tests of this milk showed that it contained a comparatively small number of antirachitic units as judged by the standard rat assay. In view of the excellent clinical results it is evident that the established method of assay cannot be relied on to appraise the value of irradiated milk for infants. This discrepancy in standardization also was found to hold true for tests of milk from cows that had been fed irradiated yeast. The indications for various antirachitic agents is variable. The most outstanding are irradiated milk either fluid or dry, milk from yeast-fed cows, cod-liver oil, viosterol and irradiated yeast, and direct ultraviolet irradiation, and concentrates and combinations of these products. These measures differ not only in their specific virtue, but also in their applicability according to whether one is considering individuals or a community, whether the community is rural or urban, and at all events according to the cost of the preparation.

Studies in Status Lymphaticus and Its Relation to Anesthetic Deaths.—KEMP (*Anæsth. and Analg.*, 1932, **11**, 128) reviews clinical, physio-

logic and pathologic evidence to show that, in animals and individuals in whom enlarged thymus as well as hyperplastic mesenteric lymph glands were found at postmortem, there is definite evidence of a relatively deficient endocrine function. The glands that play the important part of being deficient are the adrenals and the thyroid group which contains the thyroid and the thymus. Pituitary and gonadal dysfunction play a less important part. He defines status lymphaticus as a relative or absolute endocrine insufficiency leading to a disturbed metabolism and an unbalanced autonomic nervous system, with the consequent liability to the sudden onset of cyanosis and shock and death from little or no apparent cause. As yet the only recognized features on postmortem are enlarged mesenteric lymphatic glands and usually a thymus that is larger than the average for the age and state of nutrition. The symptoms of this state are dyspnea, cyanotic attacks not of cardiac origin, intermittent suffocative spasms with or without fits of crying or temper, stridor, paroxysmal coughing or choking attacks, shock and collapse from seemingly insufficient cause. The dyspnea is due to an anoxemia from a sudden change in a blood stream which no longer is able to carry oxygen. This he attributes to the lack of adrenal hormone. The cyanotic attacks are attributed to the same cause. The suffocative spasms, the stridor or laryngismus stridulus he attributes to the preponderance of the parasympathetic or vagus division of the autonomic nervous system acting upon the musculature of the larynx and bronchi. He blames the same vagotonia for the paroxysmal coughing and choking attacks, and the shock, collapse and death are the end results of the disturbed metabolism and disturbed autonomic nervous system resulting from endocrine dysfunction.

The Schick Test in Infancy.—GREENGARD (*Arch. Ped.*, 1932, **49**, 526) gave 584 infants periodic Schick tests. In all 1140 tests were done on these children. He found that the positive reactions according to age groups was in strict agreement with the mass of statistics accumulated relative to the incidence of the positive reaction in infancy. The transition from a negative to a positive reaction was demonstrated in 114 of these infants. This curve demonstrated the great variability in the duration of the passive immunity in infancy. A few of the infants showed the loss of immunity as early as the first to the third month of life. In some this immunity persisted past the first year of life and after 18 months in some cases. The greatest percentage of cases showing the loss of immunity as measured by the Schick test fell in the age group of 4 to 10 months. Comparative Schick tests were carried out on a group of 100 infants and their mothers. In this group a definite lack of agreement between the tests of the newborn and their mothers was found. Sixty per cent of the newborn infants of positive mothers gave negative reactions to the Schick test and in every instance in which a positive was obtained, the reaction of the infant was much less intense than that of the mother. All the infants of negative mothers reacted negatively. He found that the incidence of the positive Schick test in infancy varied from 17.6 per cent in the newborn period to 70 per cent at 1 year of age. Almost 80 per cent of the infants had lost their immunity by the end of the ninth month. While the positive Schick test is indicative of lack of specific immunity in the newborn, the negative Schick test

is of no significance in this age period since a large proportion of infants without antitoxic immunity show no reaction to intradermal toxin. This lack of sensitivity to intradermal diphtheria toxin is demonstrated by other types of skin irritants as well, and is due to a specific lack of reactivity of the skin of the newborn or a cutaneous energy.

Erythroblastic Anemia.—Koch and Shapiro (*Am. J. Dis. Child.*, 1932, **44**, 318) state that erythroblastic anemia should be considered as a definite disease entity. It is a grave and chronic anemia with familial and racial tendencies. Chronic infections, rickets and other nutritional disorders are of no etiological importance. The onset is in early infancy and is accompanied by splenomegaly and some degree of icteric discoloration of the skin. There may be progressive enlargement of the cranial and malar bones with associated mongoloid facies. Studies of the blood frequently reveal, besides the low hemoglobin and the erythroblastosis, a leukocytosis of varying degree and often an increase of myeloid or lymphoid cells. There is evidence of increased hemolysis in the high icteric index and positive indirect van den Bergh reactions, although the fragility of the red cells is not increased. The course is not altered by any of the recognized forms of hematopoietic stimulation. The benefit of a transfusion of blood is but temporary. Following splenectomy there is a marked and sustained increase in the circulating normoblasts. This is characteristic, but general improvement is not observed.

DERMATOLOGY AND SYPHILIS

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Chemical and Electrolytic Lesions of the Mouth Caused by Artificial Dentures.—Lain (*Arch. Dermat. and Syph.*, 1932, **25**, 21) discovered upon routine examination of the mouths of 45 consecutive adults wearing full-plate dentures that 42 per cent had either stomatitis or glossitis. Most of these cases were due to neglected oral hygiene, malocclusion or trauma caused by imperfect adaptation of the plates to the alveolar processes. In several cases, however, the pathology was attributable, by a process of exclusion, to the porosity of the plates which contained free mercury sulphid and sulphur in one instance, and aluminum powder with a trace of zinc in another. Macroscopic and microscopic analysis of other offending plates showed undercuring with porosity. Another interesting group of 30 adults, whose mouths contained two or more metals of different potentialities, registered from 1 to 40 degrees of galvanic current on the microammeter. One case of a metallic upper

plate with amalgam fillings below registered a dangerously high degree of current. A large percentage of patients with two or more kinds of metallic dentures complained of symptoms, such as metallic taste, burning tongue and acute dental nerve sensations, or presented visible mucous lesions adjacent to or between metallic dentures. The author believes that these lesions are an expression of the irritation from galvanic discharges within the mouth, the saliva acting as an electrolyte.

GYNECOLOGY AND OBSTETRICS

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Period of Conception.—Ogino (*Zentralb. f. Gynäk.*, 1932, **56**, 721), of Japan, has been interested for several years in the relationship of the time of ovulation to the possibility of conception. In his present contribution, based on rather extensive clinical observations, he states that in 14 cases of pregnancy in which the day of conception was definitely known, that day was never after the period of ovulation in the menstrual cycle. In 5 fertile women observed during a period of 115 months there were 242 sexual contacts after the period of ovulation, *i. e.*, during the 11 days preceding the next expected menstrual period, without 1 instance of pregnancy. In 13 out of 14 pregnant women in whom the date of conception was known, intercourse had always occurred during the period of ovulation or within 3 days preceding it, since the spermatozoa may remain alive for 3 days in the female genitalia. In 1 patient the date of intercourse was 4 days before ovulation. He believes, therefore, that the time during which a woman may be impregnated is, as a rule, during a period of 8 days which occurs between the 12th and 19th day before the next menses. These 8 days represent a 5-day period of possible ovulation plus the 3 preceding days during which viable spermatozoa may be in the female genitalia. During the period of 20 to 24 days before the next menses (4 to 8 days before ovulation) conception is seldom possible while during the 11 days immediately preceding the menses (postovulation period) he definitely states that conception is impossible. From the practical standpoint the conception period may be figured from the last menstrual period. In the 28-day cycle this period would be from the 10th to 17th day after the beginning of the last period. When the cycle is longer or shorter than 28 days the period of conception will vary accordingly, being moved back in the longer type and forward in the shorter type. In cases where the menstrual cycle is irregular he has constructed formulas, thus: Beginning of conception period equals 10+ (minimal

cycle, 28 days). End of conception period equals 17+ (maximal cycle, 28 days). The results of these formulas express the number of days after the last period. In estimating the cycles it is necessary to take at least 12 cycles to get an average for both maximal and minimal, as 3 or 4 cycles would not be sufficient. These formulas are practically of value only to those women whose variation is not over 10 days, since the greater the variation, the less the value of the formula. For instance, in women whose cycle varies from 26 to 36 days the beginning of the conception period would be 10+ (26 − 28) or 8 days and the end of the conception period would be 17+ (36 − 28) or 25 days after the beginning of the last period. If the next cycle would be of the minimal type menses would occur on the 27th day so that there would be only 1 day between the 25th and 27th when she would be absolutely sterile. If the next cycle were of the maximal type she would have 11 days before the onset of the following period when she would be sterile. This work is very interesting from the academic standpoint, but it is doubtful whether it will be of much practical value, as in general it would seem to be rather awkward to correlate sexual desire with mathematical formulas.

Fibroids and Ovarian Cysts Complicating Pregnancy.—According to LYNCH (*California and West. Med.*, 1931, **35**, 415), when a patient who is very anxious to have children presents herself during the second or third month of pregnancy with a complicating uterine fibroid, unless the fibroid is cervical, there are four possible plans of treatment: (1) Hysterectomy, (2) induction of abortion with subsequent removal of the tumor, (3) myomectomy with or without removal of the fetus and (4) allow the woman to progress in her pregnancy and meet emergencies if they arise. After a thorough discussion of these four plans of treatment, he believes that, in general, patients without pedunculated tumors should be allowed to progress in the pregnancy if they possibly can. Nature very often overcomes difficulties that seem impregnable even to the obstetrician of widest experience, and many cases come to term. Most of the women who are seen at term with large fibroids in the fundus deliver quickly and spontaneously. If they do not deliver quickly the labor may be quite prolonged since fibroids are frequently a cause of inertia. When there is an indication for Cesarean section at term the question often arises whether it should be followed by hysterectomy or myomectomy. Hysterectomy is relatively safe, but if the patient is young it should be remembered that the fibroids often involute after delivery to such an extent as to seem to have disappeared. There is little difference of opinion as to the proper treatment of ovarian cysts discovered early in pregnancy, as they should be removed whatever their size, type or location. The fourth month of pregnancy is probably the time at which abortion is least likely to follow operation. In brief it may be stated that in dealing with fibroids complicating labor or pregnancy one must have an exceptional case if operation is required, while with ovarian tumors one must have an exceptional case if operation is not required. (The fact that about 14 per cent of all ovarian neoplasms are malignant, and that frequently malignancy cannot be recognized preoperatively, is a strong argument in favor of immediate operation in the latter group.—C. C. N.)

OPHTHALMOLOGY

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Eye Changes in Congenital Cardiac Defects With Polycythemia.—GINSBURG (*Klin. Monatsbl. f. Augenheilk.*, 1928, **81**, 591) reports the eye findings in 3 cases of congenital stenosis of the pulmonary artery with secondary polycythemia. In the first patient, a child, aged 5 years, the erythrocytes numbered 6,500,000 per c.mm. and the hemoglobin percentage was 80. Ophthalmoscopic examination revealed hyperemic disks with sharp margins, dark-colored and somewhat dilated but not tortuous veins, with a suggestion of interrupted blood stream, normal arteries, and some grayness of the peripapillary regions. In the second patient, a girl, aged 20 years, the erythrocytes numbered 7,640,000 per c.mm. and the hemoglobin percentage was 85. The eyelids and conjunctivæ were cyanotic and the skin, conjunctival and scleral veins were dilated. The optic disks were bright red with clear margins, and the peripapillary and peripheral retina had a grayish-blue tint. The retinal veins were tortuous, cyanotic, dilated to about twice their normal size and showed a broad central light reflex. The blood stream in the veins appeared interrupted in spots. The arteries were somewhat broader and darker than normal, were tortuous and showed a broad light reflex. The finer twigs of the retinal vessels were definitely dilated and visible. In the third patient, a girl, aged 16 years, the erythrocytes numbered 9,800,000 per c.mm. and the hemoglobin percentage was 90. The conjunctivæ were markedly cyanotic and showed dilated veins, more on the right. The right iris showed many new-formed vessels. A massive hemorrhage in the vitreous prevented a view of the right fundus. Secondary glaucoma was present. In the left eye the disk was bright red with clear margins. The retinal veins were markedly dilated and tortuous, were of dark violet, almost black color, and showed localized dilatations. The arteries were not dilated but were darker than normal and markedly tortuous. The retinal vessels had broad light reflexes and the smallest vessels were dilated and tortuous. Histologic examination of the eyes of Case 3 showed the marked thickening and hyalinization of the walls of the dilated vessels in the iris, ciliary body, choroid and retina. In the left eye a large hemorrhagic infarct was present in the periphery of the retina. In the right eye many vessels showed also endothelial proliferation, with narrowing and frequently obliteration of the lumen. Numerous hemorrhages were present in the retina, between the retina and the choroid, and in the vitreous. The angle of the anterior chamber was obliterated. The author concludes that the changes seen in the retina in polycythemia vera and in congenital cardiac defects with secondary poly-

cythemia are essentially the same and that the ophthalmoscopic appearance of the vessels depends in both diseases on the increase of red cells with the resultant increased viscosity and specific gravity of the blood, slowing of the circulation and disturbance of the nutrition of the vessel walls. Histologic examination of the eyes in both diseases shows degeneration of the vessel walls with resultant hemorrhages. The degree and type of the cyanosis retinæ depends on the amount of increase in the red cells and not on the type of disease causing the increase. From his findings in these 3 cases the author believes that a light reflex is present on the retinal vessels whenever they push forward or elevate the internal limiting membrane of the retina. His histologic findings in the right eye of the third case support the view that hemorrhagic glaucoma is dependent on disease of the ocular vessels and on closure of the angle of the anterior chamber by inflammatory adhesion between the root of the iris and the posterior surface of the cornea. That this closure of the angle precedes the development of glaucoma is suggested by the finding of round-cell infiltration in the tissues at the iridocorneal angle in the left nonglaucomatous eye.

Ocular Manifestations in Cranial and Intracranial Injuries.—Pfingst (*South. Med. J.*, 1932, **25**, 357) reports 2 rather unusual ocular complications of head injuries. Isolated paralysis of the superior oblique muscle of the left eye was observed in a boy, aged 11 years, following an injury which resulted in 3 linear fractures in the parieto-occipital area, 1 of which extended downward into the base. The paralysis cleared up in about 6 weeks. Right homonymous hemianopsia and left homonymous lower quadrant anopsia were found in a man, aged 48 years, who had noticed difficulty in seeing to the right immediately upon regaining consciousness after a fall on the face. The field defects were progressive. At operation a cyst containing blood-stained fluid was found deep in the substance of the occipital lobe below the calcarine fissure. Vision returned to normal after evacuation of the cyst. Hemianopsia reappeared with the refilling of the cyst and disappeared with a second emptying of the cyst. The author calls attention to the lateralizing value of a unilateral dilated pupil after head injuries. He does not believe that fundus changes appear early, though he states that it is "not unusual after 10 to 12 hours to find a general retinal edema and a slight engorgement of the veins." True choked disk is a rare symptom in fracture of the skull. Occasionally nystagmus is present, due to injury to the semicircular canals, the oculomotor center or tract, to the 4th ventricle, or to the medulla. Paralysis of an external eye muscle may occur immediately or, with delayed hemorrhage, 2 to 3 weeks after the injury. The 6th nerve is the most frequently injured. Paralyses of eye muscles usually recover in from 1 to 10 weeks. In anterior fractures of the skull extending into the optic foramen the optic nerve may be injured with resultant blindness and loss of pupillary reaction on the side of the lesion. The optic disk in such cases is normal at first, but in 2 or 3 weeks shows optic atrophy. In fractures of the middle fossa the chiasm may be injured with resultant bitemporal hemianopsia.

RADIOLOGY

UNDER THE CHARGE OF
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Cleidocranial Dysostosis. — A case of cleidocranial dysostosis is reported by KLEMMER, SNOKE and COOPER (*Am. J. Roent. and Rad. Therap.*, 1931, **26**, 710). The patient, a girl, aged 12 years, could readily approximate the deltoid eminences anteriorly, thereby decreasing the shoulder width to less than 6 inches. Her anterior and posterior fontanelles were about ½ inch in diameter; the clavicles were absent except for bilateral stumps, each 2 inches in length and attached to the sternum; the supraspinous fossæ were absent, and the fingers and toes were short and tapering.

Roentgenologic Studies in Early Lobar Pneumonia.—It is generally conceded, says UDE (*Am. J. Roent. and Rad. Therap.*, 1930, **26**, 691) that the demonstration of a triangular area of consolidation is frequently the earliest roentgenologic finding in lobar pneumonia. However, certain observers distinctly recognize "central" or "hilum" pneumonia and conceive it to be limited to the parahilar tissues without assuming the cone shape. On the other hand, Weill and Mouriguand, from a study of 350 cases, concluded that the shadow is usually triangular with its base always cortical. The author has studied 13 cases where the shadows in the anteroposterior view were of the "central" type, but in the lateral view it was found that the apparently "central" shadow was conical, posteriorly situated and had its base on the periphery of the lung. He feels, therefore, that lateral roentgenograms of so-called "hilum" or "central" pneumonia show that the term is a misnomer, that these medial shadows are in reality posterior cone-shaped consolidations, and that they may be best defined as "early posteromedial" consolidations.

Gastric Tumors.—A patient who gives a history of chronic dyspepsia and who has free hydrochloric acid in the gastric contents may, notwithstanding the latter finding, have cancer of the stomach. This patient, claims DWYER (*Radiology*, 1931, **18**, 80), is just as deserving of a detailed study to determine or rule out cancer as is one who consults a physician on account of comparatively recent gastric symptoms. Among his series of patients 38 per cent had a history of dyspepsia for 10 years, and 70 per cent had free hydrochloric acid. A benign tumor of the stomach, although rare, may be the cause of an atypical gastric complaint, with anemia, loss of weight, diarrhea or weakness. The value of careful palpation of the stomach during roentgenoscopy cannot be emphasized too strongly; otherwise polypoid tumors are likely to escape discovery.

The Roentgen Ray in the Diagnosis and Prognosis of Upper Urinary Tract Infection.—In the roentgenologic study of the kidney PLAGGEMEYER and WELTMAN (*Radiology*, 1932, **18**, 23) regard roentgenoscopic pyelography as essential. By this method overfilling of the pelvis and consequent pain to the patient can be avoided. Obscure details can be studied better than in the pyelograms. Under vision the kidney can be palpated and its mobility and the relation of calculi, tumors, etc., can be noted.

Intravenous Urography.—One hundred and twenty-three consecutive intravenous urographic examinations have been made by CUMMING (*Radiology*, 1931, **18**, 41). He has employed pyelognost, skiodan and uroselectan, and finds the last named to be most satisfactory. With all three drugs he has seen temporarily alarming reactions. He deplores a tendency among practitioners to an overenthusiasm for intravenous urography which is not shared by urologists. He feels that this method of diagnosis should not be practised by urologists and roentgenologists independently, and that general laboratories should not attempt to place lesions of the genitourinary tract by intravenous urography.

Ear Complications in Acute Craniocerebral Injuries.—Four hundred and seventy-six cases of aural bleeding or cerebrospinal fluid leakage are reported by GURDJIAN (*Radiology*, 1931, **18**, 74). The right ear was affected in 36.5 per cent, the left in 41.3 per cent and both in 20.6 per cent of the cases. In more than 93 per cent a fracture somewhere in the skull was revealed by the Roentgen ray. Most common was a fracture line in the mastoid region extending toward the occipital bone. Many had fractures in the parietal bone extending down into the middle fossa. Others had fractures in the region of the foramen magnum. A certain number of frontal sinus fractures exhibited aural bleeding.

Treatment of Superficial Fungus Infections With the Long Wave Length Roentgen Rays (Grenz Rays).—DORNE and WHITE (*Radiology*, 1932, **18**, 727) relate their experience with 22 cases additional to 30 previously reported, which were considered to be examples of superficial fungus infection and were treated with fractional doses of Grenz rays. With such dosage those infections due to yeast-like fungi responded quite uniformly, while those of hypomycetic origin showed very little improvement, if any.

Roentgen Ray Treatment of Keloidal and Hypertrophic Scars.—In the opinion of SHERMAN (*Radiology*, 1932, **18**, 754) prognosis as to the result from treatment should be guarded in every case of keloid or scar, be it ever so recent, being particularly cautious as regards the syphilitic type, the tuberculous, erosions on the face, hard lesions and lesions in the dark-skinned races. The Roentgen ray should not be pushed to the point of producing telangiectasis. Probably the most important item in the treatment of these conditions is caution, fearlessness in calling on the plastic surgeon when he is needed, and especially caution in the prognosis, as it may save embarrassment later.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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The Acid Base Equilibrium of the Blood in Psychotic Patients With Special Reference to Affective Psychoses.—APPEL, FARR and HODES (*J. Nerv. and Ment. Dis.*, 1932, **75**, 22), feeling that the usual blood chemistry determinations offer little that is helpful for understanding the neuroses and psychoses, present a study of 120 psychotic patients and 15 normal persons. In this study they show that the chemical measurements of the electrolytes and acid-base equilibrium in the blood serum by methods that have recently been developed offer little that is enlightening in regard to these conditions. They found that: (*a*) The total base content of the blood plasma in psychotic individuals is normal; (*b*) the blood chlorids in these same cases are also normal; (*c*) the carbon dioxid content of the plasma in their psychotic cases lies within normal limits except in those cases complicated by "new admission," toxic conditions, physical abnormalities or resistance to vena puncture; (*d*) the "acid residue" is increased in the involutional depressions.

Postoperative Result of a Chronic Right-sided Hematoma With Ipsolateral Pyramidal Tract Signs. — COHEN (*Arch. Neurol. and Psychiat.*, 1932, **27**, 219) presents the case of a man, aged 30 years, in whom a headache developed a few days after a fall. Three weeks later dimness of vision and weakness ensued. Six weeks after the trauma he had choked disks; he fell backward on standing or walking. There were a right central facial weakness, increased knee jerks on the right, diminished abdominal reflexes and an equivocal right plantar response. The spinal fluid pressure was 440 mm. of water. Ventricular studies showed only a few cubic centimeters of fluid from each side. An exploration was performed on the left side and nothing was found. A week later ventriculogram showed a shift to the left of the ventricles. Ten days later an exploration of the right side revealed a chronic subdural hematoma, following the removal of which there was prompt recovery.

The Meaning of the Dream.—LONDON (*J. Nerv. and Ment. Dis.*, 1932, **75**, 40) states that dreaming primarily is an outlet for our pent-up desires and ambitions. "In fact, it is a protector of sleep." But the symbolism of the dream in which sex symbolism plays an important rôle is of utmost significance. To say that sex is the only motive in dreams is to be ignorant and perverse. Many individuals remark that

they never dream. This is not so, for if it were not for the dream we would be unable to sleep. Thus persons who suffer from insomnia are the victims of conflicts between their instinctive forces and moral training; however, when these instinctive forces and moral forces are in accord successful dream work is formed and sleep is rendered more likely. The language of the dream is a picture code; it represents ideas by means of symbols. In dream life all experiences are pictorial or photographic and the images are stored in the psychovisual field of the occipital lobe. The image after reaching the retina travels by the visual fibers to the optic chiasm, then to the crus cerebri, to the primary optic centers and then by the optic radiations to the occipital lobe, where the photographic images are stored as memory. If for some reason or other the experiences are painful to our conscious part of the psyche, they are discarded from consciousness into the unconscious, the unconscious division being present in all sensory cells of the cerebrum.

Effects of Total Removal of Left Temporal Lobe in a Right-handed Person: Localization of Areas of Brain Concerned With Speech.—DANDY (*Arch. Neurol. and Psychiat.*, 1932, **27**, 221) claims that the results of cerebral extirpations in human beings show that auditory speech is located in the parietal lobe, that visual speech is entirely distinct and separate anatomically from auditory speech, and that Broca's area occupies essentially the area described by Broca, except that it is possibly a little more posterior. To support these statements the author presents 3 cases: (*a*) A man, aged 21 years, in whom the entire left temporal lobe was removed. Four months after the operation there was no defect of speech that could be attributed to the extirpation of cerebral tissue, nor at any time did the patient show any auditory aphasia. (*b*) An individual in whom the entire left occipital lobe was resected, the supramarginal and supraängular gyri were included. The plane of the incision was vertical and slightly behind the postcentral gyrus. A month after the operative procedure the patient showed an absolute visual aphasia. He is unable to read a letter; he can write perfectly from dictation but cannot read anything he has written. He has no auditory aphasia. (*c*) A patient who had a constant series of Jacksonian convulsions beginning in the right side of the face. A small tumor together with a small zone of tissue was excised. The patient never recovered speech, so that he had a total motor aphasia but no sensory aphasia.

A Peculiar Type of Polyneuritis.—A FOREIGN LETTER (*J. Am. Med. Assn.*, 1932, **98**, 246) states that Dr. TerBraak gives observations in 10 cases of polyneuritis that developed in Amsterdam, in women, during the space of 3 months, and characterized by: (1) Predilection for groups of muscles of the extremities and well delimited; (2) symmetry of the phenomena; (3) absence of objective disorders of sensibility; (4) abolition of the Achilles reflex and persistence of the patellar reflex. In 9 cases it was established with certainty that the women had, from 10 to 20 days before the onset of the disease, made use of the same or similar means of inducing abortion. Every other cause appeared to be excluded. A similarity between this group of cases, clinically homogeneous and of a special type, with other epidemic cases

described in the forepart of 1930 in the United States under the name of "ginger paralysis" and due to the use of an adulterated extract of Jamaica ginger was observable; there is a still greater similarity to the cases of polyneuritis formerly but not now so generally known, caused by creosote phosphate, a remedy formerly much recommended by charlatans for tuberculosis.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Influence of the Parenterally Introduced Aorta Wall Cell Constituents on Blood Pressure and Blood Gas.—SATO (*Japanese J. Exper. Med.*, 1931, **9**, 509, 519, 527) discusses the above problem under three headings: I. Influence of the Endothelial Cell Constituents on Blood Gas. Cattle aorta endothelial cell emulsion was injected into the abdominal cavity of rabbits and the following changes in the blood gas content were observed. Doses of 0.005 to 0.01 gm. per kilogram of body weight caused temporary increase in the oxygen capacity and the oxygen content of the arterial blood, accompanied by a decrease in the carbon dioxid content; doses of 0.05 to 0.1 gm. per kilogram of body weight produced temporary changes the reverse of those cited above. II. Influence of Aorta Endothelial Cell Constituents on Blood Pressure. An extract of aorta endothelial cells in normal saline was injected into rabbits intravenously in doses of 0.001 to 0.1 gm. per kilogram of body weight. No marked change was observed in the blood pressure after small injections, but the largest injection of the extract caused the blood pressure to be lowered 10 to 20 mm. Hg. In experimenting with other tissue extracts the author found that after the injection of lung cell extract there was a marked lowering of the blood pressure. III. Influence of Aorta Muscle Cell Constituents on Blood Pressure. The tunica media of fresh cattle aorta was extracted with 20 per cent saline for 2 hours. This extract was injected into rabbits intravenously in doses of 0.005, 0.01, 0.05, 0.1 gm. per kilogram of body weight. Small quantities caused a slight lowering of the blood pressure which continued to fall gradually with increased doses of the extract. The blood pressure was lowered 24 to 40 mm. Hg by the injection of 0.1 gm. per kilogram of body weight. The lowered blood pressure returned to normal after 2 to 6 minutes. The depressant action on the blood pressure of the aorta muscle cell extract used in these experiments was not inhibited by atropin nor effected by cutting the vagus.

Bacteria in Anthracite Coal.—FARRELL and TURNER (*J. Bact.*, 1932, **23**, 155) have examined anthracite coal taken from various levels of a mine at Pottsville, Pa., as to its bacterial content. They also examined the bacterial flora of the surface waters and soil and of the water and soil of the levels from which they procured their specimens of

anthracite. They conclude that in coal which does not contain fissures and cracks no organisms are to be found; that the positive results of early experiments are due to the filtration of organisms from the surface and mine waters by fissured and porous anthracite. This is further confirmed by the observation that the organisms found in such specimens were similar to those isolated from the water and soil surrounding, consisting chiefly of a staphylococcus and a Gram-positive spore-forming bacillus.

Intranuclear and Cytoplasmic Inclusions ("Protozoan-like Bodies") in the Salivary Glands and Other Organs of Infants.—To the growing list of newly discovered inclusion bodies, FARBER and WOLBACH (*Am. J. Path.*, 1932, **8**, 123) add another example which they discovered in autopsy tissue of infants. Out of 183 infants examined 24 cases showed nuclear inclusions in the duct epithelium of the salivary glands. These inclusions are very like those described by COLE and KUTTNER (*J. Exp. Med.*, 1926, **44**, 855) in the submaxillary glands of guinea pigs and by THOMPSON (*J. Inf. Dis.*, 1932, **50**, 162) in the submaxillary glands of rats. These infants also showed cytoplasmic inclusions like those described by PEARSON (*Am. J. Path.*, 1930, **6**, 261) in the guinea pig. In 2 instances similar inclusions were found in the parotid gland while in 2 additional cases nuclear inclusions were found in epithelial-lined spaces of liver, lungs, kidneys, pancreas and thyroid. The latter bodies are like those described by VON GLAHN and PAPPENHEIMER (*Am. J. Path.*, 1925, **1**, 445) and MAGALHAES (*Arch. Path.*, 1931, **11**, 561). The authors suspect the inclusion bodies represent virus infection of the infants' tissues but they are unable to correlate the presence of the inclusions with any distinctive clinical or pathologic findings.

Yellow Fever Encephalitis of the Monkey (Macacus Rhesus).—Since Theiler discovered the virus of yellow fever to be neurotropic for mice, Sellards has shown that the mouse virus passed serially through brains of mice becomes modified in its action upon susceptible monkeys (M. rhesus), in that it will then induce a fatal encephalitis in these animals when inoculated intracerebrally, without causing the usual symptoms and hepatic changes of the original yellow fever virus. GOODPASTURE (*Am. J. Path.*, 1932, **8**, 137) reports a critical study of the histopathology of yellow fever encephalitis in mice and monkeys, the observations being made upon tissues supplied him by Sellards. In the mouse there is a diffuse cerebritis throughout the midcerebrum characterized by perivascular infiltration of round cells and the presence of abundant nuclear inclusions. The lesion in the monkey's brain is described as an acute, disseminated encephalomyelitis which resembles the pathologic picture of poliomyelitis in that there is marked destruction of ganglion cells accompanied by polymorphonuclear infiltration. Nuclear inclusions were detected with difficulty in 5 of 9 cases; these inclusions were few in number and often distinctly different morphologically from the typical intranuclear inclusions of yellow fever livers and mouse brains infected with yellow fever virus. The author concludes that the virus of mouse and monkey encephalitis represents a biologically modified strain of yellow fever virus which, in the monkey, is no longer productive of characteristic inclusion bodies.

The Nature of the Elementary Bodies in Psittacosis.—BEDSON (*Brit. J. Exp. Path.*, 1932, **13**, 65) investigated the relation of the psittacosis virus to the minute bodies found in virulent material in cases of psittacosis, the so-called elementary bodies. The virulent material used was the spleen from infected mice in which the bodies were demonstrated. Suspensions of such spleens were centrifuged and the virus was thrown down at a rate of 5000 revolutions per minute (demonstrated by intradermal titration in guinea pigs). By fractional centrifugation and washing the virus was freed from extraneous matter. The twice washed deposit contained the virus. The only particulate matter remaining in such a deposit were minute bodies similar in every respect to those seen in preparations of virulent material. The washed bodies were agglutinated specifically by an antipsittacosis serum, and fixed complement in its presence. Antimouse spleen serum was prepared and the bodies did not react in either way with this serum. The author concluded that the minute bodies were the virus.

The Relative Incidence of Human and Bovine Tubercle Bacilli in Tuberculous Meningitis in England.—The cerebrospinal fluid from 30 cases of tuberculous meningitis occurring in England in the years 1930–1931 was examined by GRIFFITH (*J. Path. and Bacteriol.*, 1932, **35**, 97). Of the 29 cases in children up to 10 years of age 20 were infected with the human tubercle bacillus and 9 with the bovine variety (31 per cent); the adult case showed bovine bacilli. Autopsies were performed on 20 of the children and the probable channel of infection determined by special examination of the regional lymph glands. In 14 the tracheobronchial glands showed the greatest enlargement and most extensive caseation; of these, 6 revealed the lungs to be primarily affected. Four cases had extensive involvement of the mesenteric glands, 1 showed tuberculous foci in the right tonsil and a cervical gland larger than the miliary lesions, and in the remaining case both the tracheobronchial and the mesenteric groups of glands were caseating. Combining the above cases and those of a previously reported series of 33, the author uses his percentage figures to estimate that in England and Wales upward of 700 persons died of tuberculosis of the central nervous system caused by bovine tubercle bacilli in each of the years, 1928, 1929 and 1930.

The Occupational Incidence of Primary Lung Cancer.—The occupations of 898 cases of primary lung cancer collected from the literature were investigated by BROCKBANK (*Quart. J. Med.*, 1932, **25**, 31). The findings suggest that the incidence is greatest among the laboring classes, although no one occupation stands out. Poison gas, tobacco smoking, road dust and motor car fumes are all possible etiologic factors. The occupations of 62 cases were investigated in some detail. Nine (14.5 per cent) seemed to have definitely dusty jobs and 18 (29 per cent) worked among gases and fumes. Four were badly gassed in the war and 9 smoked excessively. The importance of more detailed investigation of the occupations of patients suffering from this disease is stressed.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Toxoid Immunization for Diphtheria.—The epidemiology of diphtheria clearly indicates that the immunization of the preschool child is the keynote for the prevention of the disease. Students of the subject are gradually being convinced that toxoid has advantages over the toxin-antitoxin mixture for this purpose. A symposium on the problem was held at the last meeting of the American Public Health Association in Montreal by a group of experts. PARK and SCHRODER (*Am. J. Pub. Health*, 1932, **22**, 7) sum up as follows: Nontoxic diphtheria toxoid or anatoxin is undoubtedly the best preparation for young children and probably for older ones because it is the most potent and stable immunizing agent. Suitable underneutralized toxin-antitoxin is however an efficient preparation and is only a little less immunizing than toxoid, and it has the advantage of causing less nonspecific reactions in older children. It is to be remembered that in most toxin-antitoxin preparations the "toxin" is really mostly toxoid, since the toxin has been kept for a year or more. This allows it to become more stable and more efficient. It is difficult to decide which method should be preferred for older children. Each has its advantages. The use of toxoid mixed with lanolin, and rubbed into the skin, has a distinct place as, for example, for children in institutions or in cases in which there are objections to the use of the "needle." Alum, 0.1 or 0.2 per cent, added to the toxoid adds to its immunizing power, as is also the case when it is added to toxin-antitoxin, only then to a much less extent. It is of the greatest importance that the toxoid should be made from highly potent toxin and that the antigenic units should be stated on the containers. If it is diluted, this should be stated on the label. Toxin-antitoxin should be properly standardized and have the desired toxicity. In large cities such as New York we find toxin-antitoxin has an advantage in older children, for the injection acts not only as an immunizing dose, and gives on the average less local reaction, but because it is also a substitute for the Schick test. The exclusion of the negatively reacting children cuts down the number of later injections. For the second and third injections in these older children, either toxin-antitoxin or toxoid may be used. A Schick retest 3 to 4 months after making the immunizing injection is always desirable but not essential, for only in this way can we be absolutely sure that the desired effect has been obtained. HARRISON (*Ibid.*, p. 17) summarizes the advantages of toxoid over toxin-antitoxin mixture as follows: It is from 20 to 30 per cent more effective, even when only 2 doses are given.

It contains no serum or other animal protein likely to sensitize to a later therapeutic serum injection. It is absolutely without local or general reaction in practically all children under 7 years of age. Reactions in older children and adults are only unpleasant, not dangerous. It contains no free toxin. It is more stable, retaining its effectiveness for a longer period, and is not affected by freezing. FITZGERALD *et al.* (*Ibid.*, p. 25) state that the results in Hamilton, with a population of 150,000, and Brantford, with a population of 18,000, may be quoted as examples of municipalities that have practically eliminated diphtheria. Other experiences such as that in Windsor might also be quoted. Data from the province of Manitoba recently presented by Jackson suggest that widespread immunization in that province is a factor which accounts for the unprecedentedly low figures of diphtheria in the past year and the first months of this year. The efficiency and practicability of toxoid, properly prepared, as an immunizing agent against diphtheria, is established. POVITZKY (*Ibid.*, p. 29) states that the National Institute of Health in Washington has issued definite minimum requirements for the production and administration of toxoid, namely, the original toxin should not contain less than 5+ liters per cubic centimeter; the maximum dose should not exceed 1 cc. of the undiluated toxoid. The toxoid must protect at least 80 per cent of guinea pigs for 10 days when injected with the initial human dose against 5 m.l.d.'s.

Intestinal Carriers of Cl. Tetani and Immunity.—COLEMAN (*Am. J. Hyg.*, 1931, **14**, 515) states that, in the past at least, the incidence of postoperative tetanus in gynecologic operations has been very high. The area involved is especially liable to contaminations of intestinal origin. This together with the many instances given in the literature of postoperative tetanus after laparotomies on carrier patients, assuming that modern sterilization procedures for catgut are entirely adequate, can be lead to the conclusion that the carrier state (transient or established unknown) does not immunize against tetanus. It is furthermore highly probable, at least in the majority of these postoperative abdominal infections, that the causative organism is the one harbored in the intestines. This would tend to controvert the assumption and more particularly the experimental evidence given by Tenbroeck and Bauer that type specific immunity is conferred by intestinal carriers. It must be admitted, however, that these authors stress the fact that this immunity occurs only in guinea pigs which have been carriers during a period of several months. In the present study the author fed tetanus spores to guinea pigs over a considerable period and failed to establish them in the digestive tract after 6 months. Neither antitoxin nor agglutinins for the type fed were produced in the serum of animals. The serum of these animals showed no prophylactic value against tetanus spores when injected into other guinea pigs. The animals so fed were no more immune to the intramuscular injection of spores of the type fed than were normal controls.

The Effect of Heat, Storage and Chlorination on the Toxicity of Staphylococcus Filtrates. — JORDAN, DACK and WOOLPERT (*J. Prev. Med.*, 1931, **5**, 383) have amply demonstrated the toxicity of certain

staphylococcus filtrates when swallowed by man. A few preliminary attempts to test heat resistance seemed to indicate that the toxic substance was destroyed by boiling and weakened at lower temperatures (60° to 65° C.). In these tests the number of volunteers was necessarily limited, and a low dosage was used in each instance to avoid provoking a too serious reaction. At that time also the variations in the susceptibility of human volunteers toward the toxic substance were not fully appreciated. For these reasons early experiments gave results which later were recognized as somewhat misleading. Individual susceptibility is quite marked. It sometimes happens that when 2 men are given equivalent doses of an untreated staphylococcus filtrate, 1 is severely affected, the other not at all. This is particularly likely to occur if the amount given is kept close to the threshold of a possible reaction. In early tests it happened in most instances that the volunteer given heated filtrate was affected either not at all or less violently than the control volunteer given the same filtrate unheated. More extensive experience has shown that, in view of the natural variations in susceptibility, the conclusions drawn from a limited number of feeding experiments must be modified. The authors have made a number of additional observations which have shown that in some instances staphylococcus filtrates boiled for 30 minutes have produced typical and severe symptoms of this type of food poisoning. They conclude that the toxic substance is not completely destroyed at this time and temperature. Some diminution in toxic power may, however, possibly be caused by heating, even at temperatures below 100° C. Similarly, the toxic quality does not disappear after storage at a low temperature for as long as 67 days, but is perhaps somewhat weakened. Contact for 3 minutes with a rather strong dose of chlorin did not destroy the toxic quality.

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